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# The Lancet

## Considerations and Methods for Placebo Controls in Surgical Trials: State of the Art Review and ASPIRE Guidance --Manuscript Draft--

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<b>Abstract:</b>	<p>Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of surgical interventions. The aim of this paper is to provide a summary of current knowledge on placebo controls in surgical trials.</p> <p>A placebo control is a complex type of comparison group and, although powerful, presents many challenges in a surgical setting. This review outlines what a placebo-surgical control entails and our understanding of the placebo phenomenon in the context of surgery. It considers when placebo-surgical controls are acceptable (and when they are desirable) in terms of ethical arguments and regulatory requirements, how a placebo-surgical control should be designed, how to identify and mitigate risk for participants in placebo surgical trials, how such trials should be conducted and interpreted.</p> <p>Use of placebo control is justified in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale. Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that results of a trial would be associated with high risk of bias, particularly due to the placebo effect. Feasibility work is recommended to optimise RCT design and conduct. This review forms an outline for best practice and provides guidance, in the form of the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) checklist, for those considering the use of a placebo-control in a surgical randomised controlled trial.</p>

# CONSIDERATIONS AND METHODS FOR PLACEBO CONTROLS IN SURGICAL TRIALS

## STATE OF THE ART REVIEW AND ASPIRE GUIDANCE

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## ABSTRACT

Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of surgical interventions. The aim of this paper is to provide a summary of current knowledge on placebo controls in surgical trials.

A placebo control is a complex type of comparison group and, although powerful, presents many challenges in a surgical setting. This review outlines what a placebo-surgical control entails and our understanding of the placebo phenomenon in the context of surgery. It considers when placebo-surgical controls are acceptable (and when they are desirable) in terms of ethical arguments and regulatory requirements, how a placebo-surgical control should be designed, how to identify and mitigate risk for participants in placebo surgical trials, how such trials should be conducted and interpreted.

Use of placebo control is justified in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale. Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that results of a trial would be associated with high risk of bias, particularly due to the placebo effect. Feasibility work is recommended to optimise RCT design and conduct. This review forms an outline for best practice and provides guidance, in the form of the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) checklist, for those considering the use of a placebo-control in a surgical randomised controlled trial.

## INTRODUCTION & BACKGROUND

Compelling evidence of efficacy and safety should underpin all routine clinical therapies, ideally based on data from randomised controlled trials (RCT), and surgical therapies are no exception. Whilst an RCT comparing surgical treatment to **no** surgical treatment provides evidence of overall efficacy, it fails to account for certain biases, especially placebo. These potential biases are

particularly high for surgical interventions, where placebo effects have been shown to have substantial magnitude and duration, often amplified by the particular context of surgical care <sup>1,2</sup>. A surgical placebo control can be used to minimise bias but its use can be controversial as it poses potential risk to the patient with reduced potential benefit and presents ethical, design and trial conduct challenges.

Previous reviews have been conducted of placebo-controlled surgical trials <sup>2-4</sup> including their use, issues of recruitment and feasibility, and impact on outcome and serious adverse events <sup>5,6</sup>. These reviews have not, however, explicitly considered issues of trial design such as definition and content of placebo, when it is appropriate to use (or not use) a placebo control in a surgical trial, what factors should guide the choice of a placebo design and how that choice influences intervention standardisation. Some information on the ethical implications of surgical placebo trials is available <sup>7-12</sup>.

This review aims to provide state of the art knowledge on all aspects of placebo controls in evaluation of surgery. The insights are primarily based on the outputs of a workshop funded by the UK's National Institute of Health Research and Medical Research Council which brought together an international team of interdisciplinary experts with a strong track record of research in this field. The workshop included a systematic update of salient literature, in depth discussion of case studies and exposition of direct experience and best practice. The work culminated in the production of practical guidance for researchers; the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) checklist. We have restricted our focus to studies of adults with capacity to consent to participate in surgical research.

## WHAT IS A “PLACEBO” IN THE CONTEXT OF SURGICAL TRIALS

### *Understanding the placebo phenomenon*

Placebo effect knowledge is dominated by two main psychological theories, both of which apply to surgery. These are broadly labelled: 1) “conditioning”, a learning theory in which placebo effects are underpinned by associative learning with the placebo paired with an active treatment to trigger a physiological response; and 2) “response expectancy”, where the placebo effects are underpinned by the patient’s conscious or unconscious expectation that the placebo will have a particular effect <sup>13</sup>. Colloca and Miller integrated the learning and response expectancy theories to suggest that patient expectations are the central psychological mechanism that mediate placebo effects <sup>14</sup>. According to this model, the brain decodes the psychosocial context, formulating (conscious or unconscious) expectations about outcome that then trigger placebo responses. In turn these expectations are shaped by learning mechanisms around three types of “signs” (signs are things that convey specific meanings to individuals) in the psychosocial context <sup>15</sup>: 1) **indices** which generate expectations through sensory or memory-based associations for individuals; in essence a conditioned response <sup>16</sup>; 2) **symbols**, which generate expectations through culturally-specific conventions including language, ritual and doctor-patient communication <sup>17</sup>; and 3) **icons** which generate expectations through perceived similarities with the object, in short, expectations through social learning mechanisms <sup>18</sup>.

The manner in which patients are informed about the placebo control also shapes patients’ expectations. Any imbalance in the tone and quantity of information given about the benefits of the index procedure compared to that given for the placebo control can be stark and can influence outcome <sup>19</sup>.

Further work has characterised how different domains of the psychosocial context of healthcare are at play in clinical trials and may influence the response to a surgical placebo. These key domains include the treatment characteristics; the healthcare setting; clinician characteristics; patient characteristics; and the patient-clinician interaction. Examples of the ways that they may influence the placebo response is presented in Table 1.<sup>20,21</sup> With regard to the placebo response in general, it should also be noted that there is some suggestion of genetic susceptibility to placebo with biomarkers indicating at least a moderate influence of genes on placebo response<sup>22</sup>. Furthermore, a largely unexplored aspect of placebo is the geographic and cultural differences in patients that could influence a response. Both such factors would apply to surgical placebos similarly to that of pharmaceutical placebo but would also apply equally across groups in a randomised design.

### *Definition of a surgical placebo*

In this paper, surgery is defined as an invasive procedure using any access to the body (incision, natural orifice or percutaneous), includes use of instrumentation and operator skill<sup>23</sup>. One important distinction to highlight is between the concept of placebo for evaluation purposes, as in an experimental placebo control (as described in this paper), and the notion of purposely using placebo for benefit or treatment.

A clear definition of experimental placebo is lacking for surgical trials and classical definitions can introduce conceptual confusion rather than clarity. The blurred lines for *surgical* placebo are epitomised by the various descriptions in the literature. These vary from “a surgical intervention with theoretically little benefit”<sup>5</sup> to “sham” surgery (entirely simulated surgery or small superficial incision only)<sup>24</sup> to a “placebo surgical intervention”, a procedure in which presumed “active” components of the procedure or the critical surgical element have been removed<sup>25</sup>. In the latter, the “placebo surgical intervention” consists of routine delivery of most of the operation, but with exclusion of the presumptive “active component”. However, identification of, and conceptual clarity in defining the “critical surgical element” in surgery can be far from straightforward.

Rather than using the all-encompassing and generic “placebo control” to describe any form of placebo content, greater clarity can be achieved by describing the placebo control in terms of its *fidelity* or proximity to the complete surgical procedure<sup>26</sup>. Varying levels of fidelity are possible from *minimal fidelity*, in which there is little similarity to the complete surgical intervention (i.e. skin incisions only, thus resembling what surgeons would have traditionally described as a “sham” treatment) all the way to treatment with a complete set of surgical attributes, viz. *maximum fidelity* (i.e. the surgical procedure under evaluation). In between these extremes a *high fidelity* placebo may have identical surgical content and attributes to the complete surgical procedure but solely without the presumed active or critical component. A *low fidelity* placebo may have fewer surgical components and less resemble the complete surgical procedure (Table 2).

For example when evaluating the efficacy of arthroscopic subacromial decompression of the shoulder various choices for the placebo control exist. *Maximum fidelity* is the complete decompression surgery; a *high fidelity* placebo may be identical surgery but without removal of bone only; a *low fidelity* placebo may be very similar surgery but without removal of bone/soft tissue and lacking some other operative procedures i.e. just the insertion of an arthroscope; and a *minimum fidelity* treatment being surgical skin incisions only. Similarly, in a study of endoscopic radiofrequency ablation in patients with dysplastic Barrett’s esophagus the normal or maximum fidelity intervention involved ablation using a catheter. Patients randomised to the placebo intervention group underwent a lower fidelity procedure involving upper endoscopy, esophageal intubation and measurement of esophageal inner diameter only.<sup>27</sup>

It should be noted that this working framework is dependent on the theoretical premises of the operation and postulation of a “critical surgical element”. This is not always possible, especially with surgeries that create effect by a multi-modal or dependent set of procedures.

## WHEN ARE PLACEBO-SURGICAL CONTROLS ACCEPTABLE?

Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that the results of an open trial would be associated with high risk of bias.

Ethical considerations are fundamental to the decision as to whether one can use a surgical placebo control. Patients participating in a placebo controlled surgical trial are exposed to the risks of a surgical intervention that lacks the presumptive causally effective element (i.e. the critical surgical element). Participants are, therefore, potentially being exposed to some of the risks of surgery with less of the perceived benefits. Ethical standards suggest, however, that exposing research participants to such risks is allowed provided equipoise exists among the study arms, study harms have been minimised and are acceptable to the participant <sup>28,29</sup>.

The use of a placebo control in a surgical RCT is consistent with the ethical principle of beneficence provided the benefits and harms posed are reasonable and risks are offset by the social value of the study <sup>7</sup>. One way to determine whether the benefits and harms of a trial are acceptable is to perform component analysis <sup>30</sup>. In component analysis, a trial’s therapeutic procedures must be considered separately from its nontherapeutic procedures. However, in surgical placebos this separation is not straightforward as a placebo intervention lacking the critical surgical element may nonetheless induce physiological changes in the patient. Thus, we distinguish between the placebo control that includes warranted therapeutic procedures, in which the prospect of direct patient benefit is supported by evidence, and nontherapeutic procedures, in which no such warrant exists and the procedure is conducted for scientific purposes.

The analysis of benefits and harms in placebo controlled surgical trials is further complicated by the fact that the placebo control includes both warranted therapeutic and nontherapeutic procedures. To address this, a two-step ethical analysis is required. First, one must consider whether the use of any placebo control is justified i.e. whether equipoise holds in the face of a placebo control. Equipoise is defined as “a state of disagreement or uncertainty in the informed, expert medical community about the relative clinical merits of the intervention arms in a trial” <sup>31</sup>. Disagreement or uncertainty should be understood in terms of the state of evidence rather than unsubstantiated opinion. If equipoise exists, then it does not matter to the surgeon which trial arm the participant is placed into; given the state of knowledge at the beginning of the trial, both arms are deemed to be broadly consistent with competent surgical care <sup>30</sup>. A placebo control is permissible to evaluate a novel surgical procedure in a condition for which there is no proven, effective surgical intervention. Additionally, the case for placebo control design for surgery becomes stronger when the evidence base supporting a procedure in common use is poor, such as for vertebroplasty <sup>32</sup>. Although the surgical procedure is commonly used, equipoise exists because of the lack of supporting evidence.<sup>32</sup> Thus, in both cases, the use of a placebo control is consistent with equipoise because there is sufficient uncertainty over whether surgery offers any advantage over non surgical management alone.

If placebo is justified, then the appropriate level of fidelity to the surgical intervention must then be considered. To make this determination, two standards are relevant <sup>30</sup>. First, the harms posed by the intervention must be minimized. Second, the risks posed by the placebo intervention must be



outweighed by the value of the knowledge generated. The first standard asks us to consider whether the risks are necessary; the second standard asks us to consider whether the risks are proportionate to scientific value. Research ethics committees commonly struggle with the assessment of scientific value, and use of the “value-validity framework” is recommended.<sup>33</sup> The assessment of scientific value requires that (1) the research question is clinically important, (2) the hypothesis is justified by the current state of evidence, and (3) the study is well situated in a research portfolio.<sup>33</sup>

Lastly, the issue of patient consent is foremost in any discussion of placebo surgical trials. Surgical trials with a placebo control are inherently complex studies and conveying clearly to prospective participants what is at stake is a challenge. There is a threat from so-called therapeutic misconception, whereby research participants systematically misunderstand research elements, such as randomization or placebos as being designed to benefit them directly<sup>34</sup>. Full disclosure is therefore imperative to ensure the patient is aware that they may receive a surgical intervention omitting the presumptive critical surgical element. Informed consent must clearly identify which procedures hold the evidence-based prospect of direct benefit (where such evidence exists) and which are primarily performed to further science only. Inter alia, it is important that surgical placebos are not described in therapeutic terms, such as “treatment” or “active” procedures, when there is no clinical indication for the placebo procedure. However, communication to the patient is also required on the well-founded doubts about the efficacy of the ‘real’ procedure, most often the reason for conducting the trial in the first place.

As placebo surgical trials provide a potentially nontherapeutic intervention additional protections may be indicated. It is important to ensure adequate patient comprehension of the likely (lack of) benefit from placebo allocation to reduce therapeutic misconception.

A variety of techniques have been shown to enhance comprehension in informed consent for research, including enhanced consent forms (i.e. simplified forms developed by an interdisciplinary team involving end-users) and additional discussion time<sup>35</sup>. There is preliminary evidence that the modality (verbal, written, audio-visual) and who (e.g., the treating surgeon or an independent researcher) presents the information may also make a difference to potential trial participants in placebo surgical trials<sup>36</sup>. Formal testing of participant understanding of key elements of consent, especially relevant to the potential participation in a placebo arm, may serve to enhance comprehension and document understanding<sup>35</sup>.

There are many arguments around the balance of the cost and financial impact to design, conduct, report and disseminate the findings of a placebo surgery controlled randomized trial versus the continued performance of the surgery in question without high level evidence. This is an ethical subject in itself, however, without such a study, ineffective surgery may continue with costs and resource consumption, crowding out more effective treatments, and with risk to patients for little or no benefit.

#### *How have placebo surgical trials been used?*

We undertook a systematic review to update the latest published literature on surgical placebo rationale and methods<sup>37</sup>. The methods are shown in Text Box 1 and more details provided in Supp App 1. The review updated and extended a previously reported systematic review<sup>3</sup> until December 2017. Data were extracted for trial characteristics and methodological areas of interest, including: i) Rationale for use of placebo interventions; ii) Patient information; iii) Intervention standardisation and fidelity; iv) Delivery of co-interventions and anaesthesia; v) Trials offering treatment interventions to patients allocated to placebo; vi) How risk is minimised because of the invasive

placebo. The findings of the review have been written up for publication separately but a brief summary of findings is given below.

Fifty articles were added giving a new total of 96 placebo-surgical RCTs. Most were for gastrointestinal indications (n=40, 42%) evaluating minimally-invasive luminal endoscopic interventions (n=44, 46%). Over two thirds randomised fewer than 100 patients (n=65, 68%) and approximately a third were conducted at a single site (n=31, 32%).

The most common reason given for using placebo interventions was to quantify placebo effects (in response to perceived limitations of previous non-placebo-controlled trials and known/expected placebo effects associated with the surgical procedure under evaluation). Information provided to patients was variable. A small number of trials reported minimal information about standardisation and fidelity of interventions. Two thirds matched anaesthesia protocols between treatment and placebo groups and nearly half of trials offered treatment to placebo patients on conclusion of the trial.

Reporting of the placebo surgery was limited and variable. This suggests there is a need for clearer and more consistent reporting of rationales for placebo use, patient information provision, standardisation and fidelity of interventions, and the use of co-interventions.

#### *How should a placebo-surgical intervention be designed?*

An in-depth understanding of the presumed critical surgical element is essential for placebo trial design. Assessment of any potential risks to patients and strategies to ensure the placebo effectively mimics the treatment is also required. As part of the project, we developed a framework to optimise the design and delivery of placebo-surgical interventions in RCTs. The DITTO (Deconstruct, Identify, Take out, Think risk, Optimise) framework was developed from the systematic review of published literature and built on a previously published typology<sup>38</sup> which facilitates the deconstruction of any invasive intervention. Full details of the framework have been published separately<sup>39</sup>. In brief, the DITTO framework suggests five stages are required in the formulation of a placebo-surgical intervention (Table 3). Stage 3 of DITTO, involving identification of the critical surgical element, is exemplified by an RCT evaluating the use of endobronchial valves in patients with chronic obstructive pulmonary disease. The full fidelity treatment intervention involved endobronchial valves placed bronchoscopically to occlude all segmental bronchi of the target lobe. Patients randomised to the placebo group underwent diagnostic bronchoscopy only without valve placement as this was deemed the critical surgical element of the procedure.<sup>40</sup>

#### *Who is the placebo-surgical trial being designed to inform?*

When designing a placebo-surgical trial, it is important to identify at the outset who the trial is attempting to inform. This will influence the overall design of the study including decisions as to whether a third, no-treatment arm should also be included and which outcomes to include.

Policymakers divide into two broad groups – those who issue guidance about how interventions should be used in health care, and those who commission services and pay for them (or reimburse patients in an insurance based model). In most health systems the people who make decisions about service provision strive to maximise the health returns they get for their health care investment. They may value information about the placebo effect of an intervention differently to clinicians and/or patients.

Often guideline producers want to understand how a health gain is generated, and often feel uneasy when a gain is mainly generated through a non-specific placebo mechanism rather than the

anticipated anatomical, physiological and psychological processes that the intervention's logic model may suggest. For interventions which may have a significant placebo effect a guideline producer would like to see robust studies which explore that effect (such as a three arm study comparing active intervention, placebo, and usual care – discussed below). This enables them to explore any placebo effect which may inform the guidelines produced, will help inform a payer's decision whether to reimburse a treatment, and suggest further research to explore or modify the intervention<sup>41,42</sup>

#### *Should a placebo-surgical trial have a no intervention arm?*

There are four broad possible categories of groups (arms) in a surgical placebo trial: 1) the index surgical intervention being studied, 2) a placebo control (with varying levels of fidelity from simulated surgery/minimal skin incisions to near full fidelity); 3) non-operative care and 4) a no intervention group. The value of a no-intervention arm should always be considered.

Non-operative care has the advantage of reflecting the real-life alternatives (surgery versus a different type of treatment). The disadvantage is that it does not allow testing of any direct or placebo effect of non-critical aspects of the procedure, including patient expectations and concomitant treatments. It provides evidence for most appropriate treatment rather than fundamental efficacy.

A no intervention arm has the advantage of measuring the natural history of the condition without any treatment. It is useful to show how beneficial *any* surgery can be compared with doing nothing at all. A change in outcome may still be observed in a no intervention arm for various reasons (such as a Hawthorne effect and regression to the mean), which will also contribute to the observed effect in all groups. Nevertheless, the absence, or presence of only a modest, difference in the observed effect between surgery and no intervention would cast serious doubt on the value of the surgery regardless of the mechanism. Similar to a non-surgical control, the no intervention group cannot take account of any placebo effect due to surgery and cannot provide any information about the proposed mechanism for benefit. Whether or not the straightforward refutation of the mechanism for the effects of surgery (using a two armed comparison, placebo v normal surgery) is sufficient to conclude on surgical benefit overall remains a matter of debate.

It is argued here that a placebo trial including a no treatment comparison may be scientifically superior but considering the resource requirement, may not always be possible or justified. Two arm surgical trials can also be very useful and informative. A decision on the number and type of arms should reflect the research question and be considered in terms of sample size and analysis, ethics and trial feasibility. A study with the focus on mechanism and an assumed subsequent efficacy can positively utilise a two arm approach. A study wanting to additionally explore the value of surgery overall, regardless of mechanism, is better served by a three arm study with a no treatment control. This is despite the potential for so called “resentful demoralisation” in patients having an unarticulated or hidden preference for surgery.

Finally, in terms of trial conduct, the potential for crossover is most certainly greater in a three arm study with a no treatment control. The threat and implications of this must be weighed against the advantages stated above. A feasibility study assessing both options may be sensible before embarking on a definitive design.

## IDENTIFYING AND MITIGATING RISK IN PLACEBO SURGICAL TRIALS

The ethics literature on the use of placebo-surgical controls stresses the need for any potential risk from use of a placebo to be mitigated. The evidence on risk is mixed. The review by Wartolowska *et al.* showed that placebo-surgical controlled trials did not appear to carry any greater risk than any other treatment or control group. However, most of the placebo RCTs in that review only evaluated endoscopic or minimal access interventions. A review from the Study Center of the German Surgical Society also found that placebo-controlled serious adverse events were similar between true intervention and placebo groups and raised a concern that trials of more invasive placebo interventions might entail significant risks for study participants<sup>4</sup>. This issue is highlighted by trials such as the ORBITA study in interventional cardiology. The placebo group were in this case found to have a greater number of adverse events than the normal treatment leading to difficulties and contention in interpretation.<sup>43</sup>

Assessing risks of a placebo-surgical control, especially in relation to fidelity, is complex and difficult to quantify. Inert treatments such as low or minimum fidelity surgery may seem to have less risk than a surgical procedure with higher fidelity (in which more tissues may be involved), but this simple model may not hold. For example, those undergoing a placebo-surgical procedure, despite a priori higher risk, may still experience apparent benefit (although not achieved through any known [or theoretically causal] mechanism). Similarly, the apparent “safety” of a minimum fidelity procedure, in which there is little tissue damage, is tempered by the risk of anaesthetic complications. It should be remembered that the risk of any anaesthetic complication or surgical site infection after incision will apply to all groups undergoing surgery and similar anaesthesia (including those in the placebo arm). Discussion should include the situation when a surgical treatment's risks in a “low/minimal fidelity” placebo surgery group can potentially outweigh the benefits of the study findings to society. This can be difficult to reconcile. It is not clear how much risk is “too much” and when a placebo surgery control group trial is “not worth it”. It remains a complex area and will depend on individual procedure risk plus routine surgical risk (anaesthetic etc.) with consideration of the perceived capacity to benefit from the specific surgery in question.

Previous literature has suggested various strategies for risk mitigation including:

- Restriction of eligible patients to those with a low clinical risk profile (e.g. restriction to ASA grades 1&2)
- Reducing the invasiveness of the surgical placebo (this forms part of the balance between fidelity and risk alluded to above)
- Review of the form of anaesthesia used for the placebo-procedure
- Use of only highly experienced surgeons
- Enhanced monitoring with oversight committees

It is important, therefore, that all means of risk mitigation are explicitly outlined before undertaking a placebo control surgical trial. Where the overall risk of any placebo-surgical control is deemed to be unacceptably high (despite all possible risk mitigation strategies) a placebo-controlled design should not be used. However, without a sufficiently robust trial the surgery may continue unabated with all patients continuing to be subjected to all risks related to the procedure. In this situation, the more risky the procedure, the more urgent the need for a sufficiently robust (placebo-surgical) trial.

## TRIAL CONDUCT ISSUES FOR PLACEBO- SURGICAL TRIALS

There are a number of key considerations which must be accounted for in the trial conduct phase.

### *Nomenclature for patients*

The nomenclature for patients in placebo-surgical trials is important and patient representatives are uneasy with descriptors such as “deception” and “sham” for surgical evaluation <sup>44</sup>. Whilst such terms may often be seen in a scientific or trial design context, they are less acceptable to patients due to their negative connotations and should be avoided.

### *Informed consent*

As identified earlier, as placebo-surgical trials pose an unusually high degree of nontherapeutic risk ensuring enhanced information for informed consent is important. It is proposed that consenting material would include, but not be limited to:

- A full description of the placebo-surgical procedure;
- A statement that whilst benefit may accrue through undergoing a placebo-surgical procedure, that there is no known mechanism by which the placebo surgery should result in direct benefit for the index complaint;
- Recognition that the use of the placebo-surgical procedure is for research purposes;
- The need to avoid language in the consent process that may unwittingly promote any therapeutic misconception;
- Possible risks or discomforts linked to both index and the placebo-surgical procedure

The proposed level of fidelity of the placebo control can be helpful in deciding what information should be communicated to potential placebo surgical trial participants. The concept helps avoid therapeutic misconception in trials of this type. Any information should also clearly describe the standard index surgical procedure for the condition should they not participate in the trial and outline the known benefits and risks of this standard surgery.

### *Recruitment*

Maximising recruitment for a placebo control surgical trial is an important concern. A previous systematic review found that slow recruitment, due to difficulties finding eligible patients who agree to participate, was the major barrier to successful trial completion <sup>5</sup>. The wider literature has also noted that individuals can hold inherent beliefs and preferences about surgery as an intervention per se, which may consequently affect their willingness to participate in a placebo-surgical trial although this can be measured and accommodated for <sup>45</sup>. Randomisation, however, ensures that any such confounder (and indeed any other unknown confounder) is balanced across intervention arms.

There are many reasons for poor recruitment to placebo surgical trials but the testing of treatments that are already widely accepted, available and affordable, despite an absence of high certainty evidence supporting their use, is often cited. In such a case, it has been postulated that both surgeons and patients may be reluctant to accept a 50% chance of placebo (for a two arm trial), particularly when placebo involves invasive surgery. This could be partially mitigated by inclusion of a third arm non-surgical treatment although this would increase trial complexity and cost.

Strategies are being developed to improve recruitment for surgical placebo trials. Recruitment communication planning is crucial. This involves identifying and engaging all relevant stakeholders, identifying where people seek treatment and information, developing and testing tailored messages and creative materials, selecting appropriate delivery channels and messengers, and monitoring and evaluating process and performance. Donovan *et al.* <sup>46</sup> have developed the Quintet Recruitment Intervention for optimising recruitment and informed consent into trials based upon identification of the motivators and barriers for trial participation. Increasingly, business models and modern

marketing theory and techniques have also been used to inform strategies for recruitment <sup>47-49</sup>. The idea is to achieve public buy-in by highlighting prestige and legitimacy, both signalling worthiness of the placebo design. Empirical work has shown that when well informed, patients can be willing to take part in placebo-surgical trials and highlight many positive reasons for doing so<sup>44</sup>

Although it is known that the preferences of patients and health professionals, including surgeons, can have a decisive influence upon trial recruitment <sup>50</sup> many questions remain unanswered <sup>51</sup>. These include whether transmission of preference can be mitigated if consent is obtained by trained and ideally neutral recruiters; whether well-informed patients are more or less likely to accept randomisation; and whether or not surgeons should be allowed to restrict randomisation to eligible patients only when personally uncertain as to which intervention would be the best option for an individual patient <sup>50</sup>. Patient engagement is also critical to the future value and success of placebo controlled surgical trials. In particular, patient representatives can help with identifiable issues such as the ‘unblinding’ stage and how patients know both when and how they can access this information.

One of the strategies observed in the recent review was to offer participants randomised to the placebo control group the ‘active’ intervention once the primary endpoint for that individual has been assessed. Whilst this approach appears ethical and is commonly used, it essentially exposes the patient to more risk (i.e. the risks associated with the placebo surgery and then from an unproven intervention). For this reason, (and unless clinician autonomy appropriately overrides trial convention) the offering of the definitive treatment should likely be reserved until after a final analysis.

The issue of quality control also arises for the surgical procedure. If information on mechanism is required (and it mostly is from these studies) then the surgery should have a definite minimum quality and be performed by experienced surgeons. The “can it work” question tends to trump the “does it work” question and this mandates the use of highly competent surgeons. Evaluation of surgical quality of all surgeries performed in such studies may be needed for validation.

#### *Involvement and engagement of other key stakeholders*

The public needs to be better educated about surgical evidence and, despite several strong initiatives to improve the situation, there remains a lack of high quality evidence for surgical procedures. Engagement and acceptance from the public that these trials are required is essential. Previous research has highlighted the importance of identifying and engaging key stakeholders beyond the inclusion of the surgeon (e.g. patients, anaesthetists, operating theatre teams, ward nurses, health service managers, and policy-makers) from the outset <sup>6</sup>. For example, anaesthetists are key clinical stakeholders and are crucial in decisions as to how risk can be minimised in the placebo-surgical intervention. The peri-operative period is where the greatest risk to patients lies in placebo trials and therefore the area where the greatest focus comes from clinical, ethical, regulatory and other risk management stakeholders.

## INTERPRETATION AND TRANSLATION INTO CHANGE OF POLICY AND PRACTICE

In over half of the placebo controlled trials of surgery so far reported in the peer reviewed literature the results have shown no benefit of the definitive procedure over the placebo control <sup>3</sup>. In many others the placebo effect remains strong but sits alongside a small but genuine treatment effect from the procedure. The presence of some effect from the index procedure is, perhaps, not surprising bearing in mind the ethical and academic justifications required for the use of a surgical placebo control. Justifications must include some reasonable preliminary evidence that part or all of the treatment effect of the surgical procedure under investigation might be due the placebo effect.

The investigators responsible for undertaking and reporting such trials must, therefore, anticipate that the results of the trial will be disruptive to accepted clinical care pathways and guidelines. Investigators should also expect, and be prepared for, push-back and resistance from clinicians and patients whose beliefs and convictions are being challenged by the results. Such trials will also generate interest from other stakeholders including payers (state and insurance based), press and the media. There may be an argument to call for an increase in the use of placebo controls for RCTs in surgery to elucidate mechanisms and eliminate redundant procedures.

Experience with placebo controlled trials of knee arthroscopy suggest there can be a significant lag between evidence becoming available to a significant change in practice. In the case of knee arthroscopy for osteoarthritis the original publication was in 2002 yet it has taken 15 years for the findings to be partially adopted <sup>24</sup>. Similar resistance from the clinical community has been encountered with trials of vertebroplasty for osteoporosis <sup>52</sup> and, more recently, subacromial decompression for shoulder pain <sup>25</sup>. Consistent features of the resistance are, firstly, a belief by members of the surgical community that the patients recruited to the trial do not represent the usual population undergoing the procedure and, secondly, an assertion that the surgeons involved in the trial were not sufficiently expert in the procedure. In other words, the trial results “do not apply to me and my practice”. An illustrative example of this was the response from 15 combined Surgical Associations of a single country to the CSAW placebo-controlled trial for subacromial decompression surgery <sup>25</sup> which stated that “contrary to previous reports, the CSAW trial does not provide any new insights” and “for [this institution’s] Health System there are no consequences from the CSAW study”. In contrast, the National Health Service in the UK, short of de-implementing subacromial decompression, moved to categorise the procedure where it can only be provided if pre-conditions are met.

In anticipation of these issues, it is important to plan for the implementation and impact of findings with full engagement of all the relevant stakeholders, from the outset including key leaders in patient groups, professional associations and clinical communities involved in routinely delivering the treatment under investigation. If the results are likely to have global implications then an international approach to evaluation should be adopted. Insights from implementation science are also particularly relevant in this regard, with a range of theory-informed and evidence-based strategies available to help address expected barriers to behaviour change <sup>53</sup>.

Once the results are known, then the implications for shared decision-making and clinical practice should be explored. Advice for patients should include information about the likely benefits of both the definitive and alternative treatments.

## KEY MESSAGES

Our review has described how placebo controls may justifiably be used in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale for the study. A surgical placebo control is not appropriate for all evaluations of surgery. They may be best reserved for operations associated with lower surgical complication risk, potentially low efficacy, unjustified usage, and where a significant placebo response is expected. Against a complex set of ethical issues, it is particularly important that these trials have the greatest possible chance to answer the primary research question in a robust manner (high internal validity) with high generalizability for the relevant clinical community (high external validity). New surgical procedures of unknown value should also be evaluated and may benefit from placebo control investigation. It is important, however, that they are designed appropriately and that any risks associated with the placebo-surgical control procedure are mitigated. Considering levels of fidelity to the index surgical procedure provides a useful lens through

which to conceptualise the construction of a surgical placebo together with associated benefits and risks. A practical checklist (ASPIRE – **A**pplying **S**urgical **P**lacebo **I**n **R**andomised **E**valuations checklist), which summarises the learning points from the review and represents a minimum standard which researchers should attain and demonstrate when designing a placebo-surgical trial, is presented in Figure 1.

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**Table 1: Influences of different domains of the psychosocial context of healthcare on the placebo response**

Contextual domain	Example relevant to placebo-surgery
<b>Treatment characteristics</b>	A placebo-surgical control that is highly similar in its characteristics to the “real” procedure may influence participants’ response to the placebo procedure
<b>Healthcare setting</b>	Having a placebo-surgical procedure conducted in an operating theatre, with all the enhanced procedures that entails, might affect participants’ response to the placebo
<b>Clinician characteristics</b>	Participants’ placebo response may be influenced by the perceived high status of the practitioner (the surgeon) performing the placebo procedure
<b>Patient characteristics</b>	A patient’s previous experience of undergoing surgery and how it affected them might influence their response to a surgical placebo
<b>Patient-clinician interaction</b>	Where the surgeon has detailed and extensive interaction with the patient, this may influence their level of response to the surgical placebo

**Table 2: Levels of fidelity to the complete surgical intervention for placebo surgical trial design.**

<b>Fidelity</b>		<b>Descriptor</b>
The index procedure		Complete surgical intervention as specified for evaluation in an RCT
<b>PLACEBO</b>	<b>High</b> fidelity	Near complete attributes of the index procedure
	<b>Medium</b> fidelity	Intermediate attributes of the index procedure
	<b>Low</b> fidelity	Few attributes of the index procedure
No surgery control		No attributes of the index procedure.

**Table 3: Stages of the DITTO framework**

DITTO Stage	Description
Stage 1	<b><u>Deconstruct the treatment intervention, including the co-interventions.</u></b> The updated typology is used to deconstruct the treatment intervention resulting in a comprehensive list of treatment components and steps, including co-interventions.
Stage 2	<b><u>Identify the critical surgical element;</u></b> The critical surgical element (which could be one or more components or steps) in the surgical intervention is established and thus which treatment components/steps are included or not in the placebo intervention.
Stage 3	<b><u>Take out the critical surgical element:</u></b> The critical element is omitted from the proposed placebo intervention.
Stage 4	<b><u>Think risk and feasibility</u></b> Once the critical surgical element has been omitted it is important to take account of potential risk to patients, feasibility and the role of the placebo intervention within the RCT (e.g. as a control intervention to elucidate treatment mechanism). This may result in further components or steps being omitted from the placebo intervention.
Stage 5	<b><u>Optimise placebo:</u></b> The use of placebo optimisation strategies are to be considered throughout the design process (e.g. sensory masking).

Text box 1. Methods used in the systematic review of placebo-controlled trials of surgery

### **Systematic review methods<sup>†</sup>**

#### **Eligibility criteria**

Articles reporting RCTs (including long-term follow ups and protocols) comparing an invasive procedure with a placebo procedure in living humans were included. Pilot RCTs retrieved by the review update search were included as a source of potentially useful information about methods. Interventional procedures that change the anatomy and requires a skin incision or the use of endoscopic techniques were included. 'Placebo' referred to a surgical placebo, a sham surgery, or a procedure intended to mimic the active intervention. Excluded were RCTs that assessed medicinal products or dental interventions, non-randomised studies, reviews, editorials, letters and conference abstracts.

#### **Searches conducted**

Articles identified in a previous review [Wartolowska 2016] published between database inception and 14th of November 2014 were included (n=63). Searches using the same search terms and electronic databases (Ovid MEDLINE, Ovid EMBASE and CENTRAL) were conducted to identify RCTs published from 15th November to 31st December 2017. Additional articles, with no restriction on publication date, were identified by hand searching references of included articles and expert knowledge.

#### **Screening articles**

All articles retrieved from the current search (November 15th – December 31st 2017) were imported into an Endnote database (EndnoteTM, version X8.0.2). Titles and abstracts were screened for eligibility and full texts of potentially eligible articles were retrieved to confirm eligibility. Screening was conducted independently by two reviewers.

<sup>†</sup>Cousins S, Blencowe NB, Tsang C, et al. Reporting of key methodological issues in placebo-controlled randomised trials of invasive procedures, including surgery, needs improvement: a systematic review. *J Clin Epidemiol.* 2020 [Revisions submitted]

**Figure 1: ASPIRE checklist for the design and conduct of placebo-surgical controls in randomised trials**

ASPIRE Checklist
<p><b>Rationale &amp; ethics:</b></p> <ul style="list-style-type: none"> <li>✓ Justify the scientific rationale for the use of a placebo-surgical control</li> <li>✓ Justify how the use of placebo adheres to accepted ethical principles: <ul style="list-style-type: none"> <li>○ Is there equipoise?</li> <li>○ Is it evaluating a novel surgical procedure in a condition for which there is no proven, effective surgical intervention or is it evaluating a procedure in common use for which the evidence base is poor?</li> </ul> </li> <li>✓ Weigh up the risk-benefit considerations underpinning the choice of a placebo-controlled design</li> </ul>
<p><b>Design:</b></p> <ul style="list-style-type: none"> <li>✓ Identify who the trial is designed to inform (and thus whether the inclusion of a no intervention arm is also desirable)</li> <li>✓ Identify the critical surgical element through adoption of the DITTO framework (using pilot and feasibility work as appropriate)</li> <li>✓ Outline the placebo-surgical control in terms of its level of fidelity to the index surgical procedure</li> <li>✓ Provide a clear and detailed description of the components of the placebo-surgical intervention</li> <li>✓ Outline how mitigation of risk of the placebo-surgical control has been considered</li> <li>✓ Engage key stakeholders (including patients, anaesthetists, physiotherapists and primary care physicians) in the design of the trial</li> </ul>
<p><b>Conduct:</b></p> <ul style="list-style-type: none"> <li>✓ Avoid the use of terms such as “sham” or “fake” surgery</li> <li>✓ Engage participants in the production of the trial including patient information</li> <li>✓ Provide the following information in patient information leaflets: <ul style="list-style-type: none"> <li>○ a full description of the placebo and index surgical procedure</li> <li>○ a statement that whilst benefit may accrue through undergoing a placebo-surgical procedure, that there is no known mechanism by which the placebo surgery should result in direct benefit for the indicated complaint</li> <li>○ recognition that the use of the placebo-surgical procedure is being used predominantly for research purposes</li> <li>○ information on the possible risks or discomforts linked to the index and placebo-surgical procedure</li> </ul> </li> <li>✓ In patient information leaflets, surgical placebos should not be described in terms that may unwittingly lead participants to believe that the placebo-surgery brings benefit in and of itself</li> <li>✓ Ensure balance in the information provided on both the index surgical procedure and the placebo-surgical procedure</li> <li>✓ Consider use of enhanced processes (eg decision-aids) to facilitate patient understanding of the pros and cons for them of participating in a placebo-surgical trial</li> <li>✓ Consider use of enhanced recruitment processes (eg Quintet-type approaches) to facilitate and optimise recruitment processes</li> <li>✓ Consider enhanced monitoring of the trial to allow early stopping if benefit or harms clearly observed early in the index surgical procedure group</li> </ul>



- ✓ Consider action and communication to the patient at the end of the trial i.e. offer of different treatment

**Interpretation & Translation:**

- ✓ Prepare in advance for dissemination and implementation of findings from the trial
- ✓ Ensure early inclusion of key leaders from patient groups, professional associations and clinical communities, systematic reviewers/guideline makers, policy makers involved in routinely delivering the treatment under investigation
- ✓ Consider insights from implementation science for the effective translation of trial findings into change of practice (eg use of theory-informed, evidence-based strategies to address expected barriers to behaviour change)
- ✓ Consider the implications for shared decision-making and clinical practice early - including advice for patients about what alternative treatments are available if the implications are that it is anticipated that the procedure will be performed much less frequently as a result of the trial findings.

# CONSIDERATIONS AND METHODS FOR PLACEBO CONTROLS IN SURGICAL TRIALS STATE OF THE ART REVIEW AND ASPIRE GUIDANCE

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## ABSTRACT

Placebo comparisons are increasingly being considered for randomised trials assessing the efficacy of surgical interventions. The aim of this paper is to provide a summary of current knowledge on placebo controls in surgical trials.

A placebo control is a complex type of comparison group and, although powerful, presents many challenges in a surgical setting. This review outlines what a placebo-surgical control entails and our understanding of the placebo phenomenon in the context of surgery. It considers when placebo-surgical controls are acceptable (and when they are desirable) in terms of ethical arguments and regulatory requirements, how a placebo-surgical control should be designed, how to identify and mitigate risk for participants in placebo surgical trials, how such trials should be conducted and interpreted.

Use of placebo control is justified in randomised controlled trials of surgical interventions provided there is a strong scientific and ethical rationale. [Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that results of a trial would be associated with high risk of bias, particularly due to the placebo effect. Surgical placebos are most suited to surgical procedures that improve quality of life with a large subjective component.](#) Feasibility work is recommended to optimise RCT design and conduct. This review forms an outline for best practice and provides guidance, in the form of the ASPIRE (Applying Surgical Placebo in Randomised Evaluations) checklist, for those considering the use of a placebo-control in a surgical randomised controlled trial.

## INTRODUCTION & BACKGROUND

Compelling evidence of efficacy and safety should underpin all routine clinical therapies, ideally based on data from randomised controlled trials (RCT), and surgical therapies are no exception. Whilst an RCT comparing surgical treatment to *no* surgical treatment provides evidence of overall

86 efficacy, it fails to account for certain biases, especially placebo. These potential biases are  
87 particularly high for surgical interventions, where placebo effects have been shown to have  
88 substantial magnitude and duration, often amplified by the particular context of surgical care <sup>1,2</sup>. A  
89 surgical placebo control can be used to minimise bias but its use can be controversial as it poses  
90 potential risk to the patient with reduced potential benefit and presents ethical, design and trial  
91 conduct challenges.

92 Previous reviews have been conducted of placebo-controlled surgical trials <sup>2-4</sup> including their use,  
93 issues of recruitment and feasibility, and impact on outcome and serious adverse events <sup>5,6</sup>. These  
94 reviews have not, however, explicitly considered issues of trial design such as definition and content  
95 of placebo, when it is appropriate to use (or not use) a placebo control in a surgical trial, what  
96 factors should guide the choice of a placebo design and how that choice influences intervention  
97 standardisation. Some information on the ethical implications of surgical placebo trials is available <sup>7-  
98 12</sup>.

99 This review aims to provide state of the art knowledge on all aspects of placebo controls in  
100 evaluation of surgery. The insights are primarily based on the outputs of a workshop funded by the  
101 UK's National Institute of Health Research and Medical Research Council which brought together an  
102 international team of interdisciplinary experts with a strong track record of research in this field. The  
103 workshop included a systematic update of salient literature, in depth discussion of case studies and  
104 exposition of direct experience and best practice. The work culminated in the production of practical  
105 guidance for researchers; the ASPIRE (Applying Surgical Placebo in Randomised Evaluations)  
106 checklist. We have restricted our focus to studies of adults with capacity to consent to participate in  
107 surgical research.

## 108 WHAT IS A "PLACEBO" IN THE CONTEXT OF SURGICAL TRIALS

### 109 *Understanding the placebo phenomenon*

110 Placebo effect knowledge is dominated by two main psychological theories, both of which apply to  
111 surgery. These are broadly labelled: 1) "conditioning", a learning theory in which placebo effects are  
112 underpinned by associative learning with the placebo paired with an active treatment to trigger a  
113 physiological response; and 2) "response expectancy", where the placebo effects are underpinned  
114 by the patient's conscious or unconscious expectation that the placebo will have a particular effect  
115 <sup>13</sup>. Colloca and Miller integrated the learning and response expectancy theories to suggest that  
116 patient expectations are the central psychological mechanism that mediate placebo effects <sup>14</sup>.  
117 According to this model, the brain decodes the psychosocial context, formulating (conscious or  
118 unconscious) expectations about outcome that then trigger placebo responses. In turn these  
119 expectations are shaped by learning mechanisms around three types of "signs" (signs are things that  
120 convey specific meanings to individuals) in the psychosocial context <sup>15</sup>: 1) **indices** which generate  
121 expectations through sensory or memory-based associations for individuals; in essence a  
122 conditioned response <sup>16</sup>; 2) **symbols**, which generate expectations through culturally-specific  
123 conventions including language, ritual and doctor-patient communication <sup>17</sup>; and 3) **icons** which  
124 generate expectations through perceived similarities with the object, in short, expectations through  
125 social learning mechanisms <sup>18</sup>.

126 The manner in which patients are informed about the placebo control also shapes patients'  
127 expectations. Any imbalance in the tone and quantity of information given about the benefits of the  
128 index procedure compared to that given for the placebo control can be stark and can influence  
129 outcome <sup>19</sup>.

Further work has characterised how different domains of the psychosocial context of healthcare (including the setting, clinician characteristics, etc.) are at play in clinical trials and may influence the response to a surgical placebo. These key domains include the treatment characteristics; the healthcare setting; clinician characteristics; patient characteristics; and the patient-clinician interaction. Examples of the ways that they may influence the placebo response is presented in (Table 1).<sup>20,21</sup> With regard to the placebo response in general, it should also be noted that there is some suggestion of genetic susceptibility to placebo with biomarkers indicating at least a moderate influence of genes on placebo response<sup>22</sup>. Furthermore, a largely unexplored aspect of placebo is the geographic and cultural differences in patients that could influence a response. Both such factors would apply to surgical placebos similarly to that of pharmaceutical placebo but would also apply equally across groups in a randomised design.

#### Definition of a surgical placebo

In this paper, surgery is defined as an invasive procedure using any access to the body (incision, natural orifice or percutaneous), includes use of instrumentation and operator skill<sup>23</sup>. One important distinction to highlight is between the concept of placebo for evaluation purposes, as in an experimental placebo control (as described in this paper), and the notion of purposely using placebo for benefit or treatment.

A clear definition of experimental placebo is lacking for surgical trials and classical definitions can introduce conceptual confusion rather than clarity. The blurred lines for *surgical* placebo are epitomised by the various descriptions in the literature. These vary from “a surgical intervention with theoretically little benefit”<sup>5</sup> to “sham” surgery (entirely simulated surgery or small superficial incision only)<sup>24</sup> to a “placebo surgical intervention”, a procedure in which presumed “active” components of the procedure or the critical surgical element have been removed<sup>25</sup>. In the latter, the “placebo surgical intervention” consists of routine delivery of most of the operation, but with exclusion of the presumptive “active component”. However, identification of, and conceptual clarity in defining the “critical surgical element” in surgery can be far from straightforward.

Rather than using the all-encompassing and generic “placebo control” to describe any form of placebo content, greater clarity can be achieved by describing the placebo control in terms of its *fidelity* or proximity to the complete surgical procedure<sup>26</sup>. Varying levels of fidelity are possible from *minimal* ~~no~~ *fidelity*, in which there is little similarity to the complete surgical intervention (i.e. skin incisions only, ~~and thus resembling what surgeons would have traditionally described as a “sham”~~ *treatment*) all the way to treatment with a complete set of surgical attributes, viz. *maximum fidelity* (i.e. the surgical procedure under evaluation). In between these extremes, a *high fidelity* placebo may have identical surgical content and attributes to the complete surgical procedure but *solely* without the presumed active or critical component. A *low fidelity* placebo may have fewer surgical components and ~~less more closely resemble the complete surgical procedure what surgeons would have traditionally described as a “sham” treatment~~ (Table 2).

For example when evaluating the efficacy of arthroscopic subacromial decompression of the shoulder various choices for the placebo control exist. *Maximum fidelity* is the complete decompression surgery; a *high fidelity* placebo may be identical surgery but without removal of bone *only*; a *low fidelity* placebo may be *very similar identical* surgery but without removal of bone ~~or~~ soft tissue *and lacking some other operative procedures i.e.;* just the insertion of an arthroscope; and a *minimum* ~~or no~~ *fidelity* treatment being surgical skin incisions only. *Similarly, in a study of endoscopic radiofrequency ablation in patients with dysplastic Barrett’s esophagus the normal or maximum fidelity intervention involved ablation using a catheter. Patients randomised to the*

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175 placebo intervention group underwent a lower fidelity procedure involving upper endoscopy,  
176 esophageal intubation and measurement of esophageal inner diameter only.<sup>27</sup>  
177 It should be noted that this working framework is dependent on the theoretical premises of the  
178 operation and postulation of a “critical surgical element”. This is not always possible, especially with  
179 surgeries that create effect by a multi-modal or dependent set of procedures.

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Commented [DB4]: R10

## 180 WHEN ARE PLACEBO-SURGICAL CONTROLS ACCEPTABLE?

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181 Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the  
182 procedure and a justified concern that the results of an open trial would be associated with high risk  
183 of bias. Surgical placebos may be most appropriate where the benefits of surgery are not life saving,  
184 but involve improvement in quality of life with a significant subjective component.

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185 Ethical considerations are fundamental to the decision as to whether one can use a surgical placebo  
186 control. Patients participating in a placebo controlled surgical trial are exposed to the risks of a  
187 surgical intervention that lacks the presumptive causally effective element (i.e. the critical surgical  
188 element). Participants are, therefore, potentially being exposed to some of the risks of surgery with  
189 less of the perceived benefits. Ethical standards suggest, however, that exposing research  
190 participants to such risks is allowed provided equipoise exists among the study arms, study harms  
191 have been minimised and are acceptable to the participant<sup>28,29</sup>.

192 The use of a placebo control in a surgical RCT is consistent with the ethical principle of beneficence  
193 provided the benefits and harms risks posed are reasonable and risks are offset by the social value of  
194 the study<sup>7</sup>. One way to determine whether the benefits and harms of a trial are acceptable is to  
195 perform component analysis<sup>30</sup>. In component analysis, a trial’s therapeutic procedures must be  
196 considered separately from its nontherapeutic procedures. However, in surgical placebos this  
197 separation is not straightforward as a placebo intervention lacking the critical surgical element may  
198 nonetheless induce physiological changes in the patient. Thus, we distinguish between the placebo  
199 control that includes warranted therapeutic procedures, in which the prospect of direct patient  
200 benefit is supported by evidence, and nontherapeutic procedures, in which no such warrant exists  
201 and the procedure is conducted for scientific purposes.

202 The analysis of benefits and harms in placebo controlled surgical trials is further complicated by the  
203 fact that the placebo control includes both warranted therapeutic and nontherapeutic procedures.  
204 To address this, a two-step ethical analysis is required. First, one must consider whether the use of  
205 any placebo control is justified i.e. whether clinical equipoise holds in the face of a placebo control.  
206 Clinical ~~e~~Equipoise is defined as “a state of disagreement or uncertainty in the informed, expert  
207 medical community about the relative clinical merits of the intervention arms in a trial”<sup>31</sup>.  
208 Disagreement or uncertainty should be understood in terms of the state of evidence rather than  
209 unsubstantiated opinion. If equipoise exists, then it does not matter to the surgeon which trial arm  
210 the participant is placed into; given the state of knowledge at the beginning of the trial, both arms  
211 are deemed to be broadly consistent with competent surgical ~~medical~~ care<sup>30</sup>. A placebo control is  
212 permissible to evaluate a novel surgical procedure in a condition for which there is no proven,  
213 effective surgical intervention. Additionally, the case for placebo control design for surgery becomes  
214 stronger when the evidence base supporting a procedure in common use is poor, such as for  
215 vertebroplasty<sup>32</sup>. Although the surgical procedure is commonly used, equipoise exists because of the  
216 lack of supporting evidence.<sup>32</sup> Thus, in ~~in~~ both cases, the use of a placebo control is consistent with  
217 clinical ~~e~~equipoise because there is sufficient uncertainty over whether surgery offers any advantage  
218 over medical-non surgical management alone.

219 If placebo is justified, then the appropriate level of fidelity to the surgical intervention must then be  
220 considered. To make this determination, two standards are relevant<sup>30</sup>. First, the harms posed by the  
221 intervention must be minimized. Second, the risks posed by the placebo intervention must be  
222 outweighed by the value of the knowledge generated. The first standard asks us to consider whether  
223 the risks are necessary; the second standard asks us to consider whether the risks are proportionate  
224 [to scientific value. Research ethics committees commonly struggle with the assessment of scientific](#)  
225 [value, and use of the “value-validity framework” is recommended.](#)<sup>33</sup> [The assessment of scientific](#)  
226 [value requires that \(1\) the research question is clinically important, \(2\) the hypothesis is justified by](#)  
227 [the current state of evidence, and \(3\) the study is well situated in a research portfolio.](#)<sup>33</sup>.

Commented [DB7]: R14

228 Lastly, the issue of patient consent is foremost in any discussion of placebo surgical trials. Surgical  
229 trials with a placebo control are inherently complex studies and conveying clearly to prospective  
230 participants what is at stake is a challenge. There is a threat from so-called therapeutic  
231 misconception, whereby research participants systematically misunderstand research elements,  
232 such as randomization or placebos as being designed to benefit them directly<sup>34</sup>. Full disclosure is  
233 therefore imperative to ensure the patient is aware that they may receive a surgical intervention  
234 omitting the presumptive critical surgical element. Informed consent must clearly identify which  
235 procedures hold the evidence-based prospect of direct benefit (where such evidence exists) and  
236 which are primarily performed to further science only. Inter alia, it is important that surgical  
237 placebos are not described in therapeutic terms, such as “treatment” or “active” procedures, when  
238 there is no clinical indication for the placebo procedure. However, communication to the patient is  
239 also required on the well-founded doubts about the efficacy of the ‘real’ procedure, most often the  
240 reason for conducting the trial in the first place.

241 [As ~~some~~ placebo surgical trials provide ~~use~~ an unusually high degree of a potentially nontherapeutic](#)  
242 [intervention~~risk~~, additional protections may be indicated. It is important to ensure adequate patient](#)  
243 [comprehension of the likely \(lack of\) benefit from placebo allocation to reduce therapeutic](#)  
244 [misconception.](#)

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245 A variety of techniques have been shown to enhance comprehension in informed consent for  
246 research, including enhanced consent forms (i.e. simplified forms developed by an interdisciplinary  
247 team involving end-users) and additional discussion time<sup>35</sup>. There is preliminary evidence that the  
248 [modality medium](#) (verbal, written, audio-visual) and who (e.g., the treating surgeon or an  
249 independent researcher) presents the information may also make a difference to potential trial  
250 participants in placebo surgical trials<sup>36</sup>. Formal testing of participant understanding of key elements  
251 of consent, especially relevant to the potential participation in a placebo arm, may serve to enhance  
252 comprehension and document understanding<sup>35</sup>.

253 [There are many arguments around the balance of the cost and financial impact to design, conduct,](#)  
254 [report and disseminate the findings of a placebo surgery controlled randomized trial versus the](#)  
255 [continued performance of the surgery in question without high level evidence. This is an ethical](#)  
256 [subject in itself, however, without such a study, ineffective surgery may continue with costs and](#)  
257 [resource consumption, crowding out more effective treatments, and with risk to patients for little or](#)  
258 [no benefit.](#)

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259

260 *How have placebo surgical trials been used?*

261 We undertook a systematic review to update the latest published literature on surgical placebo  
262 rationale and methods<sup>37</sup>. [The methods](#) are [shown](#) in Text Box 1 and more details provided in Supp

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263 App 1. The review updated and extended a previously reported systematic review<sup>3</sup> until December  
264 2017. Data were extracted for trial characteristics and methodological areas of interest, including: i)  
265 Rationale for use of placebo interventions; ii) Patient information; iii) Intervention standardisation  
266 and fidelity; iv) Delivery of co-interventions and anaesthesia; v) Trials offering treatment  
267 interventions to patients allocated to placebo; vi) How risk is minimised because of the invasive  
268 placebo. The findings of the review have been written up for publication separately but a brief  
269 summary of findings is given below.

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270 Fifty articles were added giving a new total of 96 placebo-surgical RCTs. Most were for  
271 gastrointestinal indications (n=40, 42%) evaluating minimally-invasive luminal endoscopic  
272 interventions (n=44, 46%). Over two thirds randomised fewer than 100 patients (n=65, 68%) and  
273 approximately a third were conducted at a single site (n=31, 32%).

274 The most common reason given for using placebo interventions was to quantify placebo effects (in  
275 response to perceived limitations of previous non-placebo-controlled trials and known/expected  
276 placebo effects associated with the surgical procedure under evaluation). Information provided to  
277 patients was variable. A small number of trials reported minimal information about standardisation  
278 and fidelity of interventions. Two thirds matched anaesthesia protocols between treatment and  
279 placebo groups and nearly half of trials offered treatment to placebo patients on conclusion of the  
280 trial.

281 Reporting of the placebo surgery was limited and variable. This suggests there is a need for clearer  
282 and more consistent reporting of rationales for placebo use, patient information provision,  
283 standardisation and fidelity of interventions, and the use of co-interventions.

284 *How should a placebo-surgical intervention be designed?*

285 An in-depth understanding of the presumed critical surgical element is essential for placebo trial  
286 design. Assessment of any potential risks to patients and strategies to ensure the placebo effectively  
287 mimics the treatment is also required. As part of the project, we developed a framework to optimise  
288 the design and delivery of placebo-surgical interventions in RCTs. The DITTO ([Deconstruct, Identify,](#)  
289 [Take out, Think risk, Optimise](#)) framework was developed from the systematic review of published  
290 literature and built on a previously published typology<sup>38</sup> which facilitates the deconstruction of any  
291 invasive intervention. Full details of the framework have been published separately<sup>39</sup>. In brief, the  
292 DITTO framework suggests five stages are required in the formulation of a placebo-surgical  
293 intervention (Table 3). [Stage 3 of DITTO, involving identification of the critical surgical element, is](#)  
294 [exemplified by an RCT evaluating the use of endobronchial valves in patients with chronic obstructive](#)  
295 [pulmonary disease. The full fidelity treatment intervention involved endobronchial valves placed](#)  
296 [bronchoscopically to occlude all segmental bronchi of the target lobe. Patients randomised to the](#)  
297 [placebo group underwent diagnostic bronchoscopy only without valve placement as this was](#)  
298 [deemed the critical surgical element of the procedure.](#)<sup>40</sup>

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299

300 *Who is the placebo-surgical trial being designed to inform?*

301 When designing a placebo-surgical trial, it is important to identify at the outset who the trial is  
302 attempting to inform. This will influence the overall design of the study including decisions as to  
303 whether a third, no-treatment arm should also be included and which outcomes to include.

304 Policymakers divide into two broad groups – those who issue guidance about how interventions  
305 should be used in health care, and those who commission services and pay for them (or reimburse



306 patients in an insurance based model). In most health systems the people who make decisions about  
307 service provision strive to maximise the health returns they get for their health care investment.  
308 They may value information about the placebo effect of an intervention differently to clinicians  
309 and/or patients.

310 ~~Producers of guidelines tend to~~ Often guideline producers want to understand how a health gain is  
311 generated, and often feel uneasy when a gain is mainly generated through a non-specific placebo  
312 mechanism rather than the anticipated anatomical, physiological and psychological processes that  
313 the intervention's logic model may suggest. ~~For interventions which may have a significant placebo~~  
314 ~~effect a guideline producer would like to see robust studies which explore that effect (such as a~~  
315 ~~three arm study comparing active intervention, placebo, and usual care – discussed below). This~~  
316 ~~enables them to partition out any placebo effect which will inform the guidelines produced.~~

317 For interventions which may have a significant placebo effect a guideline producer would like to see  
318 robust studies which explore that effect (such as a three arm study comparing active intervention,  
319 placebo, and usual care – discussed below). This enables them to explore any placebo effect which  
320 may inform the guidelines produced, will help inform a payer's decision whether to reimburse a  
321 treatment, and suggest further research to explore or modify the intervention <sup>41,42</sup>

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322 *Should a placebo-surgical trial have a no intervention arm?*

323 There are four broad possible categories of groups (arms) in a surgical placebo trial: 1) the index  
324 surgical intervention being studied, 2) a placebo control (with varying levels of fidelity from  
325 simulated surgery/minimal skin incisions to near full fidelity); 3) non-operative care and 4) a no  
326 intervention group. The value of a no-intervention arm should always be considered.

327 ~~Best-Non-operative care~~ has the advantage of reflecting the real-life alternatives (surgery versus a  
328 different type of treatment~~best non-operative care~~). The disadvantage is that it does not allow  
329 testing of any direct or placebo effect of non-critical aspects of the procedure, including patient  
330 expectations and concomitant treatments. It provides evidence for most appropriate best  
331 treatment rather than fundamental efficacy.

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332 A no intervention arm has the advantage of measuring the natural history of the condition without  
333 any treatment. It is useful to show how beneficial *any* surgery can be compared with doing nothing  
334 at all. A change in outcome may still be observed in a no intervention arm for various reasons (such  
335 as a Hawthorne effect and regression to the mean), which will also contribute to the observed effect  
336 in all groups. Nevertheless, the Absence-absence, or presence of only a modest, difference in the  
337 observed effect between surgery and no intervention would cast serious doubt on the value of the  
338 surgery regardless of the mechanism. Similar to a non-surgical control, the no intervention group  
339 cannot take account of any placebo effect due to surgery and cannot provide any information about  
340 the proposed mechanism for benefit. Whether or not the straightforward refutation of the  
341 mechanism for the effects of surgery (using a two armed comparison, placebo v normal surgery) is  
342 sufficient to conclude on surgical benefit overall remains a matter of debate.

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343 It is argued here that a placebo trial including a no treatment comparison may be scientifically  
344 superior but considering the resource requirement, may not always be possible or justified. Two arm  
345 surgical trials can also be very useful and informative. A decision on Justification for the number and  
346 type of arms should reflect the research question and be considered in terms of sample size and  
347 analysis, ethics and trial feasibility. A study with the focus on mechanism and an assumed  
348 subsequent efficacy can positively utilise a two arm approach. A study wanting to additionally  
349 explore the value of surgery overall, regardless of mechanism, is better served by a three arm study

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with a no treatment control. This is despite the potential for so called “resentful demoralisation” in patients having an unarticulated or hidden preference for surgery.

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Finally, in terms of trial conduct, the potential for crossover is most certainly greater in a three arm study with a no treatment control. The threat and implications of this must be weighed against the advantages stated above. A feasibility study assessing both options may be sensible before embarking on a definitive design.

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## IDENTIFYING AND MITIGATING RISK IN PLACEBO SURGICAL TRIALS

The ethics literature on the use of placebo-surgical controls stresses the need for any potential risk from use of a placebo to be mitigated. The evidence on risk is mixed. The review by Wartolowska *et al.* showed that placebo-surgical controlled trials did not appear to carry any greater risk than any other treatment or control group. However, most of the placebo RCTs in that review only evaluated endoscopic or minimal access interventions. A review from the Study Center of the German Surgical Society also found that placebo-controlled serious adverse events were similar between true intervention and placebo groups and raised a concern that trials of more invasive placebo interventions might entail significant risks for study participants <sup>4</sup>. This issue is highlighted by trials such as the ORBITA study in interventional cardiology. The placebo group were in this case found to have a greater number of adverse events than the normal treatment leading to difficulties and contention in interpretation.<sup>43</sup>

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Assessing risks of a placebo-surgical control, especially in relation to fidelity, is complex and difficult to quantify. Inert treatments such as low or minimum fidelity surgery may seem to have less risk than a surgical procedure with higher fidelity (in which more tissues may be involved), but this simple model may not hold. For example, those undergoing a placebo-surgical procedure, despite a priori higher risk, may still experience apparent benefit (although not achieved through any known [or theoretically causal] mechanism). Similarly, the apparent “safety” of a minimum fidelity procedure, in which there is little tissue damage, is tempered by the risk of anaesthetic complications. It should be remembered that the risk of any anaesthetic complication or surgical site infection after incision will apply to all groups undergoing surgery and similar anaesthesia (including those in the placebo arm). Discussion should include the situation when a surgical treatment's risks in a “low/minimal fidelity” placebo surgery group can potentially outweigh the benefits of the study findings to society. This can be difficult to reconcile. It is not clear how much risk is “too much” and when a placebo surgery control group trial is “not worth it”. It remains a complex area and will depend on individual procedure risk plus routine surgical risk (anaesthetic etc.) with consideration of the perceived capacity to benefit from the specific surgery in question. Low fidelity interventions also have a greater risk of unblinding.

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Previous literature has suggested various strategies for risk mitigation including:

- Restriction of eligible patients to those with a low clinical risk profile (e.g. restriction to ASA grades 1&2)
- Reducing the invasiveness of the surgical placebo (this forms part of the balance between fidelity and risk alluded to above)
- Review of the form of anaesthesia used for the placebo-procedure
- Use of only highly experienced surgeons
- Enhanced monitoring with oversight committees

It is important, therefore, that all means of risk mitigation are explicitly outlined before undertaking a placebo control surgical trial. Where the overall risk of any placebo-surgical control is deemed to

394 be unacceptably high (despite all possible risk mitigation strategies) a placebo-controlled design  
395 should not be used. However, without a sufficiently robust trial the surgery may continue unabated  
396 with all patients continuing to be subjected to all risks related to the procedure. In this situation, the  
397 more risky the procedure, the more urgent the need for a sufficiently robust (placebo-surgical) trial.

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## 398 TRIAL CONDUCT ISSUES FOR PLACEBO- SURGICAL TRIALS

399 There are a number of key considerations which must be accounted for in the trial conduct phase.

### 400 *Nomenclature for patients*

401 The nomenclature for patients in placebo-surgical trials is important and patient representatives are  
402 uneasy with descriptors such as “deception” and “sham” for surgical evaluation <sup>44</sup>. Whilst such terms  
403 may often be seen in a scientific or trial design context, they are less acceptable to patients due to  
404 their negative connotations and should be avoided.

### 405 *Informed consent*

406 As identified earlier, as placebo-surgical trials pose an unusually high degree of nontherapeutic risk  
407 ensuring enhanced information for informed consent is important. It is proposed that consenting  
408 material would include, but not be limited to:

- 409 • A full description of the placebo-surgical procedure;
- 410 • A statement that whilst benefit may accrue through undergoing a placebo-surgical procedure,  
411 that there is no known mechanism by which the placebo surgery should result in direct benefit  
412 for the index complaint;
- 413 • Recognition that the use of the placebo-surgical procedure is for research purposes;
- 414 • The need to avoid language in the consent process that may unwittingly promote any  
415 therapeutic misconception;
- 416 • Possible risks or discomforts linked to both index and the placebo-surgical procedure

417 The proposed level of fidelity of the placebo control can be helpful in deciding what information  
418 should be communicated to potential placebo surgical trial participants. The concept helps avoid  
419 therapeutic misconception in trials of this type. Any information should also clearly describe the  
420 standard index surgical procedure for the condition should they not participate in the trial and  
421 outline the known benefits and risks of this standard surgery.

### 422 *Recruitment*

423 Maximising recruitment for a placebo control surgical trial is an important concern. A previous  
424 systematic review found that slow recruitment, due to difficulties finding eligible patients who agree  
425 to participate, was the major barrier to successful trial completion <sup>5</sup>. The wider literature has also  
426 noted that individuals can hold inherent beliefs and preferences about surgery as an intervention  
427 per se, which may consequently affect their willingness to participate in a placebo-surgical trial  
428 although this can be measured and accommodated for <sup>45</sup>. Randomisation, however, ensures that any  
429 such confounder (and indeed any other unknown confounder) is balanced across intervention arms.

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430 There are many reasons for poor recruitment to placebo surgical trials but the testing of treatments  
431 that are already widely accepted, available and affordable, despite an absence of high certainty  
432 evidence supporting their use, is often cited. In such a case, it has been postulated that both  
433 surgeons and patients may be reluctant to accept a 50% chance of placebo (for a two arm trial),

434 particularly when placebo involves invasive surgery. This could be partially mitigated by inclusion of  
435 a third arm non-surgical treatment although this would increase trial complexity and cost.

436

437 Strategies are being developed to improve recruitment for surgical placebo trials. Recruitment  
438 communication planning is crucial. This involves identifying and engaging all relevant stakeholders,  
439 identifying where people seek treatment and information, developing and testing tailored messages  
440 and creative materials, selecting appropriate delivery channels and messengers, and monitoring and  
441 evaluating process and performance. Donovan *et al.*<sup>46</sup> have developed the Quintet Recruitment  
442 Intervention for optimising recruitment and informed consent into trials based upon identification  
443 of the motivators and barriers for trial participation. Increasingly, business models and modern  
444 marketing theory and techniques have also been used to inform strategies for recruitment<sup>47-49</sup>. The  
445 idea is to achieve public buy-in by highlighting prestige and legitimacy, both signalling worthiness of  
446 the placebo design—. Empirical work has shown that when well informed, patients can be willing to  
447 take part in placebo-surgical trials and highlight many positive reasons for doing so<sup>44</sup>. Empirical work  
448 has shown, that when well informed, patients can be willing to take part in placebo surgical trials  
449 and highlight many positive reasons for doing so

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450 Although it is known that the preferences of patients and health professionals, including surgeons,  
451 can have a decisive influence upon trial recruitment<sup>50</sup> many questions remain unanswered<sup>51</sup>. These  
452 include whether transmission of preference can be mitigated if consent is obtained by trained and  
453 ideally neutral recruiters; whether well-informed patients are more or less likely to accept  
454 randomisation; and whether or not surgeons should be allowed to restrict randomisation to eligible  
455 patients only when personally uncertain as to which intervention would be the best option for an  
456 individual patient<sup>50</sup>. Patient engagement is also critical to the future value and success of placebo  
457 controlled surgical trials. In particular, patient representatives can help with identifiable issues such  
458 as the 'unblinding' stage and how patients know both when and how they can access this  
459 information.

460 One of the strategies observed in the recent review was to offer participants randomised to the  
461 placebo control group the 'active' intervention once the primary endpoint for that individual has been  
462 assessed. Whilst this approach appears ethical and is commonly used, it essentially exposes the  
463 patient to more risk (i.e. the risks associated with the placebo surgery and then from an unproven  
464 intervention). For this reason, (and unless clinician autonomy appropriately overrides trial convention)  
465 the offering of the definitive treatment should likely be reserved until after a final analysis.

466 The issue of quality control also arises for the surgical procedure. If information on mechanism is  
467 required (and it mostly is from these studies) then the surgery should have a definite minimum  
468 quality and be performed by experienced surgeons. The "can it work" question tends to trump the  
469 "does it work" question and this mandates the use of highly competent surgeons. Evaluation of  
470 surgical quality of all surgeries performed in such studies may be needed for validation.

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471 *Involvement and engagement of other key stakeholders*

472 The public needs to be better educated about surgical evidence and, despite several strong initiatives  
473 to improve the situation, there remains a lack of high quality evidence for surgical procedures.  
474 Engagement and acceptance from the public that these trials are required is essential. Previous  
475 research has highlighted the importance of identifying and engaging key stakeholders beyond the  
476 inclusion of the surgeon (e.g. patients, anaesthetists, operating theatre teams, ward nurses, health  
477 service managers, and policy-makers) from the outset<sup>6</sup>. For example, anaesthetists are key clinical

478 stakeholders and are crucial in decisions as to how risk can be minimised in the placebo-surgical  
479 intervention. The peri-operative period is where the greatest risk to patients lies in placebo trials and  
480 therefore the area where the greatest focus comes from clinical, ethical, regulatory and other risk  
481 management stakeholders.

## 482 INTERPRETATION AND TRANSLATION INTO CHANGE OF POLICY AND PRACTICE

483 In over half of the placebo controlled trials of surgery so far reported in the peer reviewed literature  
484 the results have shown no benefit of the definitive procedure over the placebo control <sup>3</sup>. In many  
485 others the placebo effect remains strong but sits alongside a small but genuine treatment effect from  
486 the procedure. The presence of some effect from the index procedure is, perhaps, not surprising  
487 bearing in mind the ethical and academic justifications required for the use of a surgical placebo  
488 control. Justifications must include some reasonable preliminary evidence that part or all of the  
489 treatment effect of the surgical procedure under investigation might be due the placebo effect.

490 The investigators responsible for undertaking and reporting such trials must, therefore, anticipate that  
491 the results of the trial will be disruptive to accepted clinical care pathways and guidelines.  
492 Investigators should also expect, and be prepared for, push-back and resistance from clinicians and  
493 patients whose beliefs and convictions are being challenged by the results. Such trials will also  
494 generate interest from other stakeholders including payers (state and insurance based), press and the  
495 media. There may be an argument to call for an increase in the use of placebo controls for RCTs in  
496 surgery to elucidate mechanisms and eliminate redundant procedures.

497 Experience with placebo controlled trials of knee arthroscopy ~~suggest there can be has-revealed-a~~  
498 ~~significant~~~~long~~ lag between evidence becoming available to a significant change in practice. In the case  
499 of knee arthroscopy for osteoarthritis the original publication was in 2002 yet it has taken 15 years for  
500 the findings to be partially adopted <sup>24</sup>. Similar resistance from the clinical community has been  
501 encountered with trials of vertebroplasty for osteoporosis <sup>52</sup> and, more recently, subacromial  
502 decompression for shoulder pain <sup>25</sup>. Consistent features of the resistance are, firstly, a belief by  
503 members of the surgical community that the patients recruited to the trial do not represent the usual  
504 population undergoing the procedure and, secondly, an assertion that the surgeons involved in the  
505 trial were not sufficiently expert in the procedure. In other words, the trial results “do not apply to me  
506 and my practice”. An illustrative example of this was the response from 15 combined Surgical  
507 Associations of a single country to the CSAW placebo-controlled trial for subacromial decompression  
508 surgery <sup>25</sup> which stated that “contrary to previous reports, the CSAW trial does not provide any new  
509 insights” and “for [this institution’s] Health System there are no consequences from the CSAW study”.  
510 In contrast, the National Health Service in ~~the UK~~~~another country~~, short of de-implementing  
511 subacromial decompression, moved to categorise the procedure where it can only be provided if pre-  
512 conditions are met.

513 In anticipation of these issues, it is important to plan for the implementation and impact of findings  
514 with full engagement of all the relevant stakeholders, from the outset including key leaders in patient  
515 groups, professional associations and clinical communities involved in routinely delivering the  
516 treatment under investigation. If the results are likely to have global implications then an international  
517 approach to evaluation should be adopted. Insights from implementation science are also particularly  
518 relevant in this regard, with a range of theory-informed and evidence-based strategies available to  
519 help address expected barriers to behaviour change <sup>53</sup>.

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520 Once the results are known, then the implications for shared decision-making and clinical practice  
521 should be explored. Advice for patients should include information about [the likely benefits of both](#)  
522 [the definitive and](#) alternative treatments.

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## 523 KEY MESSAGES

524 Our review has described how placebo controls may justifiably be used in randomised controlled trials  
525 of surgical interventions provided there is a strong scientific and ethical rationale for the study. A  
526 surgical placebo control is not appropriate for all evaluations of surgery. They may be best reserved  
527 for operations associated with lower surgical complication risk, potentially low efficacy, unjustified  
528 usage, and where a significant placebo response is expected. [Against a complex set of ethical issues,](#)  
529 [it is particularly important that these trials have the greatest possible chance to answer the primary](#)  
530 [research question in a robust manner \(high internal validity\) with high generalizability for the relevant](#)  
531 [clinical community \(high external validity\).](#) New surgical procedures of unknown value should also be  
532 evaluated and may benefit from placebo control investigation. It is important, however, that they are  
533 designed appropriately and that any risks associated with the placebo-surgical control procedure are  
534 mitigated. Considering levels of fidelity to the index surgical procedure provides a useful lens through  
535 which to conceptualise the construction of a surgical placebo together with associated benefits and  
536 risks. A practical checklist (ASPIRE – **A**pplying **S**urgical **P**lacebo **I**n **R**andomised **E**valuations checklist),  
537 which summarises the learning points from the review and represents a minimum standard which  
538 researchers should attain and demonstrate when designing a placebo-surgical trial, is presented in  
539 Figure 1.

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540

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551 As part of the process of developing the guidance, a two-day workshop was held in St Anne's College  
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553 Dr Jonathan Pugh, Dr Felicity Bishop, Dr Sian Cousins, Professor Charles Weijer, Prof Richard  
554 Huxtable, Professor Jon Nicholl, Dr Pascal Probst, Professor Peter Brocklehurst, Dr Andrew Cook, Dr  
555 Katie Gillies, Professor Freddie Hamdy, Professor Ian Harris, Dr Naomi Lee, Professor Stefan  
556 Lohmander, Professor Amar Rangan, Professor Barnaby Reeves, Dr Samuel Rowley.

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562 recorded the workshop discussions.

563

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The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR, the MRC or the Department of Health and Social Care. AC and JMB are NIHR Senior Investigators.

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**Table 1: Influences of different domains of the psychosocial context of healthcare on the placebo response**

Contextual domain	Example relevant to placebo-surgery
<b>Treatment characteristics</b>	A placebo-surgical control that is highly similar in its characteristics to the “real” procedure may influence participants’ response to the placebo procedure
<b>Healthcare setting</b>	Having a placebo-surgical procedure conducted in an operating theatre, with all the enhanced procedures that entails, might affect participants’ response to the placebo
<b>Clinician characteristics</b>	Participants’ placebo response may be influenced by the perceived high status of the practitioner (the surgeon) performing the placebo procedure
<b>Patient characteristics</b>	A patient’s previous experience of undergoing surgery and how it affected them might influence their response to a surgical placebo
<b>Patient-clinician interaction</b>	Where the surgeon has detailed and extensive interaction with the patient, this may influence their level of response to the surgical placebo

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811 Table 2: Levels of fidelity to the complete surgical intervention for placebo surgical trial design.

Level of fidelity to surgical intervention	Descriptor
Maximum fidelity: the index procedure—NOT placebo	The complete surgical intervention as specified for evaluation in an RCT. This is the true intervention arm of the trial.
Placebo with High Fidelity	High fidelity with the specification of the treatment intervention (near complete attributes of the procedure under investigation)
Placebo with Low Fidelity	Low fidelity with the specification of the treatment intervention (lesser attributes of the procedure under investigation)
Minimum Fidelity or Placebo with No Fidelity	Lowest or zero fidelity with the specification of the treatment intervention (i.e. sham). (No attributes of the procedure under investigation, e.g. skin incisions only)

Fidelity		Descriptor
The index procedure		Complete surgical intervention as specified for evaluation in an RCT
PLACEBO	High fidelity	Near complete attributes of the index procedure
	Medium fidelity	Intermediate attributes of the index procedure
	Low fidelity	Few attributes of the index procedure
No surgery control		No attributes of the index procedure.

Commented [DB29]: R9 (revised table)

815 **Table 3: Stages of the DITTO framework**

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DITTO Stage	Description
Stage 1	<b>Deconstruct the treatment intervention, including the co-interventions.</b> The updated typology is used to deconstruct the treatment intervention resulting in a comprehensive list of treatment components and steps, including co-interventions.
Stage 2	<b>Identify the critical surgical element;</b> The critical surgical element (which could be one or more components or steps) in the surgical intervention is established and thus which treatment components/steps are included or not in the placebo intervention.
Stage 3	<b>Take out the critical surgical element:</b> The critical element is omitted from the proposed placebo intervention.
Stage 4	<b>Think risk and feasibility</b> Once the critical surgical element has been omitted it is important to take account of potential risk to patients, feasibility and the role of the placebo intervention within the RCT (e.g. as a control intervention to elucidate treatment mechanism). This may result in further components or steps being omitted from the placebo intervention.
Stage 5	<b>Optimise placebo:</b> The use of placebo optimisation strategies are to be considered throughout the design process (e.g. sensory masking).

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Text box 1. Methods used in the systematic review of placebo-controlled trials of surgery

Commented [DB30]: R19

### Systematic review methods<sup>†</sup>

#### Eligibility criteria

Articles reporting RCTs (including long-term follow ups and protocols) comparing an invasive procedure with a placebo procedure in living humans were included. Pilot RCTs retrieved by the review update search were included as a source of potentially useful information about methods. Interventional procedures that change the anatomy and requires a skin incision or the use of endoscopic techniques were included. 'Placebo' referred to a surgical placebo, a sham surgery, or a procedure intended to mimic the active intervention. Excluded were RCTs that assessed medicinal products or dental interventions, non-randomised studies, reviews, editorials, letters and conference abstracts.

#### Searches conducted

Articles identified in a previous review [Wartolowska 2016] published between database inception and 14th of November 2014 were included (n=63). Searches using the same search terms and electronic databases (Ovid MEDLINE, Ovid EMBASE and CENTRAL) were conducted to identify RCTs published from 15th November to 31st December 2017. Additional articles, with no restriction on publication date, were identified by hand searching references of included articles and expert knowledge.

#### Screening articles

All articles retrieved from the current search (November 15th – December 31st 2017) were imported into an Endnote database (EndnoteTM, version X8.0.2). Titles and abstracts were screened for eligibility and full texts of potentially eligible articles were retrieved to confirm eligibility. Screening was conducted independently by two reviewers.

<sup>†</sup>Cousins S, Blencowe NB, Tsang C, et al. Reporting of key methodological issues in placebo-controlled randomised trials of invasive procedures, including surgery, needs improvement: a systematic review. *J Clin Epidemiol.* 2020 [Revisions submitted]

845 **Figure 1: ASPIRE checklist for the design and conduct of placebo-surgical controls in randomised**  
846 **trials**  
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ASPIRE Checklist
<p><b>Rationale &amp; ethics:</b></p> <ul style="list-style-type: none"> <li>☑ Justify the scientific rationale for the use of a placebo-surgical control</li> <li>☑ Justify how the use of placebo adheres to accepted ethical principles: <ul style="list-style-type: none"> <li>○ Is there equipoise?</li> <li>○ Is it evaluating a novel surgical procedure in a condition for which there is no proven, effective surgical intervention or is it evaluating a procedure in common use for which the evidence base is poor?</li> </ul> </li> <li>☑ Weigh up the risk-benefit considerations underpinning the choice of a placebo-controlled design</li> </ul>
<p><b>Design:</b></p> <ul style="list-style-type: none"> <li>☑ Identify who the trial is designed to inform (and thus whether the inclusion of a no intervention arm is also desirable)</li> <li>☑ Identify the critical surgical element through adoption of the DITTO framework (using pilot and feasibility work as appropriate)</li> <li>☑ Outline the placebo-surgical control in terms of its level of fidelity to the index surgical procedure</li> <li>☑ Provide a clear and detailed description of the components of the placebo-surgical intervention</li> <li>☑ Outline how mitigation of risk of the placebo-surgical control has been considered</li> <li>☑ Engage key stakeholders (including patients, anaesthetists, physiotherapists and primary care physicians) in the design of the trial</li> </ul>
<p><b>Conduct:</b></p> <ul style="list-style-type: none"> <li>☑ Avoid the use of terms such as “sham” or “fake” surgery</li> <li>☑ Engage participants in the production of the trial including patient information</li> <li>☑ Provide the following information in patient information leaflets: <ul style="list-style-type: none"> <li>○ a full description of the placebo and index surgical procedure</li> <li>○ a statement that whilst benefit may accrue through undergoing a placebo-surgical procedure, that there is no known mechanism by which the placebo surgery should result in direct benefit for the indicated complaint</li> <li>○ recognition that the use of the placebo-surgical procedure is being used predominantly for research purposes</li> <li>○ information on the possible risks or discomforts linked to the index and placebo-surgical procedure</li> </ul> </li> <li>☑ In patient information leaflets, surgical placebos should not be described in terms that may unwittingly lead participants to believe that the placebo-surgery brings benefit in and of itself</li> <li>☑ Ensure balance in the information provided on both the index surgical procedure and the placebo-surgical procedure</li> <li>☑ Consider use of enhanced processes (eg decision-aids) to facilitate patient understanding of the pros and cons for them of participating in a placebo-surgical trial</li> <li>☑ Consider use of enhanced recruitment processes (eg Quintet-type approaches) to facilitate and optimise recruitment processes</li> <li>☑ Consider enhanced monitoring of the trial to allow early stopping if benefit or harms clearly observed early in the index surgical procedure group</li> </ul>



- ✔ Consider action and communication to the patient at the end of the trial i.e. offer of different treatment

**Interpretation & Translation:**

- ✔ Prepare in advance for dissemination and implementation of findings from the trial
- ✔ Ensure early inclusion of key leaders from patient groups, professional associations and clinical communities, systematic reviewers/guideline makers, policy makers involved in routinely delivering the treatment under investigation
- ✔ Consider insights from implementation science for the effective translation of trial findings into change of practice (eg use of theory-informed, evidence-based strategies to address expected barriers to behaviour change)
- ✔ Consider the implications for shared decision-making and clinical practice early - including advice for patients about what alternative treatments are available if the implications are that it is anticipated that the procedure will be performed much less frequently as a result of the trial findings.

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## RESPONSE TO EDITOR AND REVIEWER COMMENTS

Dear Dr Lee

Thank you for the thoughtful and detailed comments provided by the reviewers. As requested, we provide a point by point response below:

Line numbers and revision point references (R) relate to the tracked change version.

### EDITOR COMMENTS:

COMMENT:	RESPONSE
Please note that not every point below will be relevant to your manuscript.	
1. Please indicate after each of the reviewers' points the text changes which have been made (if any) and the line number on the revised manuscript at which your change can be found. [Line numbers can be added to your word document using the 'page layout' tab. Please select continuous numbers.] 2. When interpreting editorial points made by reviewers, please remember we will edit the final manuscript if accepted.	Done
3. Please indicate any authors who are full professors.	Done
4. Please list the highest degree for each author (one degree only, please).	Done
5. Please check that all author name spellings and affiliations are correct.	Done
6. For randomised trials please follow the CONSORT reporting guidelines ( <a href="http://www.consort-statement.org">http://www.consort-statement.org</a> ) and CONSORT for abstracts ( <a href="http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)61835-2/fulltext">http://www.thelancet.com/journals/lancet/article/PIIS0140-6736(07)61835-2/fulltext</a> ), and include a CONSORT checklist with your resubmission.	n/a

7. Please ensure that the title of the paper is non-declamatory (ie, it describes the aim of study rather than the findings) and that it includes a description of the study type (eg, a randomised controlled trial).	Done
8. Please limit the summary to pre-defined primary endpoints and safety endpoints.	n/a
9. For RCTs, please state the trial registration number.	n/a
10. At the end of the methods section please state the role of the funder in: data collection, analysis, interpretation, writing of the manuscript and the decision to submit. Please also state which author(s) had access to all the data, and which author(s) were responsible for the decision to submit the manuscript etc.	Role of funder included at end of paper
11. Please explain any deviations from the protocol.	n/a
12. Please report all outcomes specified in the protocol.	n/a
13. If any exploratory outcomes are reported that were not pre-specified, please make it clear that these analyses were post-hoc.	n/a
14. Please use rINNs for drug names. For genes and proteins, authors can use their preferred terminology so long as it is in current use by the community, but should provide the preferred human name from Uniprot ( <a href="http://www.uniprot.org/uniprot/">http://www.uniprot.org/uniprot/</a> ) for proteins and HUGO ( <a href="http://www.genenames.org">http://www.genenames.org</a> ) for genes at first use to assist non-specialists.	n/a
15. For drug studies, please ensure that details of doses, route of delivery, and schedule are included.	n/a
16. For the main outcome measures, please include a result for each group, plus a	n/a

point estimate (eg, RR, HR) with a measure of precision (eg, 95% CI) for the absolute difference between groups, in both the Summary and the main Results section of the paper.	
17. p-values should be exact, but no longer than 4 decimal places (eg $p < 0.0001$ ). Two decimals are acceptable in tables for non-significant p-values 18. Please provide absolute numbers to accompany all percentages. Percentages should be rounded to whole numbers unless the study population is very large ( $>10\,000$ individuals).	n/a
19. Please give 95% confidence intervals for hazard ratios/odds ratios.	n/a
20. For means, please provide standard deviation (or error, as appropriate).	n/a
21. Please provide interquartile ranges for medians.	n/a
22. Please provide numbers at risk for Kaplan-Meier plots and ensure that plots include a measure of effect (eg, log-rank p); estimates should be reported with 95% CIs.	n/a
23. Please ensure that the Discussion contains a section on limitations of the study.	included
24. Please provide the text, tables, and figures in an editable format. See link above this list for details of acceptable formats for figure files.	Done
25. Our production system is not compatible with Endnotes. Please convert to normal text.	Done
26. If accepted, only 5-6 non-text items (figures, tables, or panels) can be accommodated in the print edition; additional material can be provided in a web appendix. Please indicate which items can go in a web appendix.	Done

27. Please provide a research in context panel with 3 parts: Evidence before this study (which includes a description of how you searched for evidence and how you assessed the quality of that evidence); Added value of the study; and Implications of all the available evidence.	NA unless requested
28. At the end of the manuscript, please summarise the contribution of each author to the work.	Done
29. At the end of the manuscript please summarise the declaration of interests for each author.	Completed – separate document
30. If you have not yet done so, please return all signed authorship statements and conflict of interest forms. We also require signed statements from any named person in the acknowledgements saying that they agree to be acknowledged.	Completed
31. For any personal communication, please provide a letter showing that the person agrees to their name being used.	n/a
32. As corresponding author, please confirm that all authors have seen and approved of the final text.	Confirmed
33. If your author line includes a study group, collaborators' names and affiliations may be listed at the end of the paper or in the appendix. Additionally, if you wish the names of collaborators within a study group to appear on PubMed, please upload with your revision a list of names of all study group members presented as a two-column table in Word. First and middle names or initials should be placed in the first column, and surnames in the second column. Names should be ordered as you wish them to	n/a

appear on PubMed. The table will not be included in the paper itself - it's simply used to make sure that PubMed adds the names correctly.	
34. Please note our guideline length for research articles is 3500 words and 30 references. For RCTs, the text can be expanded to 4500 words.	This is a review article with guide length 4000. The comprehensive (but important) requests from reviewers have increased the original word count.
35. From July 1, 2018, all submitted reports of clinical trials must contain a data sharing statement, to be included at the end of the manuscript or in an appendix (please provide as a separate pdf). Data sharing statements must indicate: *Whether data collected for the study, including individual participant data and a data dictionary defining each field in the set, will be made available to others; *What data will be made available (deidentified participant data, participant data with identifiers, data dictionary, or other specified data set); *Whether additional, related documents will be available (eg, study protocol, statistical analysis plan, informed consent form); *When these data will be available (beginning and end date, or "with publication", as applicable); *Where the data will be made available (including complete URLs or email addresses if relevant); *By what access criteria data will be shared (including with whom, for what types of analyses, by what mechanism - eg, with or without investigator support, after approval of a proposal, with a signed data access agreement - or any additional restrictions).	n/a

<p>Clinical trials that begin enrolling participants on or after Jan 1, 2019, must include a data sharing plan in the trial's registration. If the data sharing plan changes after registration, this should be reflected in the statement submitted and published, and updated in the registry record. For reports of research other than clinical trials, data sharing statements are encouraged but not required. Mendeley Data (<a href="https://data.mendeley.com">https://data.mendeley.com</a>) is a secure online repository for research data, permitting archiving of any file type and assigning a permanent and unique digital object identifier (DOI) so that the files can be easily referenced. If authors wish to share their supporting data, and have not already made alternative arrangements, a Mendeley DOI can be referred to in the data sharing statement.</p>	n/a
REVIEWER COMMENT	RESPONSE
REVIEWER #1	
<p>Reviewer #1: I read "Considerations and Methods for Placebo Controls in Surgical Trials: State of the Art Review and ASPIRE Guidance" by Beard and co-authors with interest. The authors have submitted a well written narrative review of the use of placebo surgery control groups in randomized trials. English language was used, easy to follow, with manuscript form and structure appropriate, three tables and one figure (none of which need color, can be black &amp; white). References were mostly up to date, with 1/3 of references</p>	<p>Thank you for your accurate summary of the paper and some excellent suggestions.</p>

published within past five years. The narrative review was a general overview of placebo surgery controls, with sufficient detail to grasp the impetus for study, and the reason for publication in The Lancet. There were no fatal flaws that should immediately preclude publication. However, there are major omissions listed below that should be added to ensure that this manuscript does truly cover all aspects of optimal quality placebo surgery controlled randomized trials in surgery. The authors added a novel checklist, ASPIRE, that can aid investigators in creation, conduct, design, interpretation, reporting, and dissemination of the study's findings. If the authors can make the requested revisions, then I would be happy to provide a re-review at any time. I thank the authors for their efforts, as I can only imagine the challenges associated with that many authors of the world's leaders on placebo surgery RCTs all writing a single manuscript and simply, concisely, and cohesively summarizing the topic - "complexity is your enemy. Any fool can make something complicated. It is hard to keep things simple". The authors did this well. I welcome a revision and would make a publication decision on their thoughtful responses. Thank you for the opportunity to participate in the peer review process with this manuscript.



<p>List of positives:</p> <ul style="list-style-type: none"> <li>• Excellent concise general overview of use of placebo surgery controls in RCT</li> <li>• Includes a discussion of the use of natural history "no treatment" control groups, in addition to placebo surgery, "real" surgery, and non-surgical care groups</li> <li>• Creation of ASPIRE checklist.</li> <li>• Good discussion of neutral members in discussions during the informed consent process and the potential bias of surgeons and non-surgical investigators (and/or decision-makers) involved in those discussions.</li> </ul>	<p>Thank you for identifying these positives.</p>
<p>List of MAJOR negatives:</p>	
<ul style="list-style-type: none"> <li>• No discussion of genetic susceptibility to placebo - the past decade has yielded several dozen high quality studies that have reported several biomarkers indicating at least a moderate influence of genes on placebo response (COMT, OPRM1).</li> </ul>	<p><b>R1:</b> Unfortunately we are word restricted and whilst this is a very interesting and worthwhile sub area of placebo science we simply do not have room to do the subject justice in this précised review. However, it should be commented upon and we have added a couple of sentences alluding to this (and indeed to other aspects that we may not have covered in depth eg. neurophysiology).</p> <p>We have tried to focus and outline surgical specific placebo aspects for this work and not become too entwined with general placebo which is already well documented.</p> <p>L135-137</p> <p><i>Text added:</i>  <i>With regard to the placebo response in general, it should also be noted that there is some suggestion of genetic susceptibility to placebo with biomarkers indicating at least a moderate influence of genes on placebo response</i></p>
<ul style="list-style-type: none"> <li>• No discussion of the selection bias of</li> </ul>	<p><b>R2:</b> A good point and mental health/psychiatric factors for selection bias are indeed worth consideration. However,</p>

<p>individuals that are willing to be randomized to a placebo surgery without mental health/psychiatric evaluation. The same mental health status that may allow an individual to participate may be the same mental health status that would portend a worse outcome following any surgical intervention - this is usually an elevated pain state, low pain threshold mental wellness disorder. This cascade of decisions motivated by pain and/or dysfunction may alter the study's ultimate conclusions.</p>	<p>empirical evidence from placebo-surgical studies suggest that patients have a variety of reasons for wishing to participate in a placebo controlled trial, and that they make sound and informed judgements when doing so. For example, extensive qualitative work undertaken with prospective participants as part of the design of the KORAL placebo surgical trial (Campbell et al, <i>Health Technology Assessment</i> 2010; <b>14</b>(5): 1-180) suggested that the majority of all eligible patients would consider participating and they highlighted a range of reasons for wishing to take part - including an expressed desire to help others; perceptions about the potential personal benefit to be gained from participation (and not solely via the intervention but also through the wider trial processes). As such, the empirical evidence does not suggest selection bias of this type is as strong as the reviewer suggests. We have added a sentence to highlight that the empirical evidence suggests participants have varied reasons for wishing to take part in a placebo-surgical trial.</p> <p><i>Added text ... “The idea is to achieve public buy-in by highlighting prestige and legitimacy, both signalling worthiness of the placebo design. Empirical work has shown that when well informed, patients can be willing to take part in placebo-surgical trials and highlight many positive reasons for doing so “</i>  — L446-450</p> <p>It has been acknowledged in the literature, however, that patients may have different inherent beliefs and preferences towards surgery in general as an intervention (which may affect their openness, and possible response, to surgical interventions in general and thus, by extension, one could argue to the placebo effect of surgery). This has been encapsulated into the validated “Beliefs about Surgery” questionnaire (Francis et al; <i>Psychol Health</i>. 2009; 24(10):1125-37). We have included a reference to this in the revised manuscript.</p> <p><i>Added text ... “The wider literature has also noted that individuals can hold inherent beliefs and preferences about surgery as an intervention per se, which may consequently affect their willingness to participate in a placebo-surgical trial - although this can be measured and accommodated for [Francis et al,2009].”</i> L425-428.</p>
<ul style="list-style-type: none"> <li>• Would like to see a little discussion on the balance of cost and financial impact to design, conduct, report, and disseminate the</li> </ul>	<p><b>R3:</b> Agree here but again limited in space for this interesting area. We have added a short paragraph.</p> <p><i>Added Text: There are many arguments around the balance of the cost and financial impact to design, conduct, report, and disseminate the findings of a placebo surgery controlled</i></p>

findings of a placebo surgery controlled randomized trial, versus the continued performance of the surgery in question without high level evidence.	<p><i>randomized trial, versus the continued performance of the surgery in question without high level evidence. This is an ethical subject in itself, however, without such a study, ineffective surgery may continue with costs and resource consumption, crowding out more effective treatments, and with risk to patients for no or little benefit.</i></p> <p><i>L253-258</i></p>
<ul style="list-style-type: none"> <li>Would like to see more discussion on the geographic and cultural differences in patients that could influence a placebo response - Finland known for sisu and grit; Denmark and Norway known for hygge; USA known for opioid epidemic. All these patient demographics clearly impact placebo response.</li> </ul>	<p><b>R4:</b> Within any randomised controlled trial, there are many known and unknown confounders that may affect response to treatment (and by extension to the placebo effect). This is well recognised in the trial methodology literature. Indeed, this is one of the main arguments in support of randomisation – as randomisation will ensure that all possible confounders are balanced across the groups.</p> <p>This would also apply across any cultural differences in trial populations – randomisation would ensure that any such effects (and indeed any other known or unknown effects) would be equalised across the groups. We have added a sentence to the manuscript to note this.</p> <p><i>Added text ... “Randomisation, however, ensures that any such confounder (and indeed any other unknown confounder) is balanced across intervention arms.”</i></p> <p><i>L428-429</i></p>
List of MINOR negatives:	
<ul style="list-style-type: none"> <li>Use of "best" nonoperative care is superfluous, ambiguous, and unnecessary - why not also call it "best" operative care - some surgeons are good, some are bad; some physical therapists are good, some are bad. This "best" descriptor implies that the non-surgical intervention is superior to something, while the surgery is just "surgery", not "best surgical treatment".</li> </ul>	<p><b>R5:</b> Agree – we have rephrased. (we mean evidence-based).</p> <p>Added text:  <i>“Non-operative care has the advantage of reflecting the real-life alternatives (surgery versus a different type of treatment). The disadvantage is that it does not allow testing of any direct or placebo effect of non-critical aspects of the procedure, including patient expectations and concomitant treatments. It provides evidence for most appropriate treatment rather than fundamental efficacy.”</i></p> <p><i>L327-328</i></p>
<ul style="list-style-type: none"> <li>Would like to see a greater discussion of the situation when a surgical</li> </ul>	<p><b>R6:</b> It should be noted that reviews of placebo surgery research have shown that the risks from placebo allocation are lower than that of the active intervention groups, and that it is</p>

<p>treatment's risks in a "no fidelity" or "low/minimal fidelity" placebo surgery group significantly outweigh the benefits to society - how does a group of researchers reconcile this issue? How much risk is too much? When is a placebo surgery control group trial "not worth it"? the example that immediately comes to mind is that of hip arthroscopy - the most rapidly growing sub-specialty in all of orthopedic surgery and musculoskeletal medicine across the world - even a low/minimal fidelity placebo group involves a very significant risk - up to 40% risk of temporary or permanent groin/perineum nerve injury (pudendal, obturator) due to traction, sex organ dysfunction, genital skin injury, iatrogenic cartilage or labral injury upon camera entry into the joint, peripheral nerve injury with portal placement (lateral femoral cutaneous nerve).</p>	<p>the benefits versus the additional risk of surgery that is being tested in placebo trials. This has been discussed in some detail already but we have added a section to enhance.</p> <p>Added text:</p> <p><i>"Discussion should include the situation when a surgical treatment's risks in a "low/minimal fidelity" placebo surgery group can potentially outweigh the benefits of the study findings to society. This can be difficult to reconcile. It is not clear how much risk is "too much" and when a placebo surgery control group trial is "not worth it". It remains a complex area and will depend on individual procedure risk plus routine surgical risk (anaesthetic etc.) with consideration of the perceived capacity to benefit from the specific surgery in question."</i></p> <p>L377-383</p>
<ul style="list-style-type: none"> <li>discusses only musculoskeletal medicine, orthopedic surgery cases, with little discussion (intra-luminal endoscopic interventions) of other aspects of medicine.</li> </ul>	<p>R7: Reasonable point although a good section of the placebo control literature involves MSK and orthopaedics.</p> <p>Examples from chest medicine (bronchoscopy) and GI surgery have been added.</p> <p>L293-298</p>
<ul style="list-style-type: none"> <li>No discussion of clinical decision-making in the situation of a patient</li> </ul>	<p>We were not entirely sure what the reviewer was asking for here and in the interests of word count have not addressed this point.</p>

<p>with "failed non-surgical treatment and continued symptoms" and published data showing placebo surgeries (and, of course, the active "real" surgery too) improve symptoms.</p>	
<ul style="list-style-type: none"> <li>No discussion of Hawthorne effect in a research design like this</li> </ul>	<p><b>R8:</b> We have inserted new text to briefly raise the issue of the Hawthorne effect. The inserted text as follows:  <i>"A change in outcome may still be observed in a no intervention arm for various reasons (such as a Hawthorne effect and regression to the mean), which will also contribute to the observed effect in all groups. Nevertheless, the absence, or the presence of only a modest difference in the observed effect between surgery and no intervention would cast serious doubt on the value of the surgery regardless of the mechanism."</i></p> <p>L334-337</p>
<ul style="list-style-type: none"> <li>Lack of consideration that a "no fidelity" (i.e. sham surgery) placebo surgery control is not truly "no fidelity", as skin incisions alone can denervate (for example, tennis elbow placebo surgery trial in Australia) and have a real physiologic effect and reduce pain.</li> </ul>	<p><b>R9:</b> Thank you. We agree with this point and have modified the text and Table 2 accordingly. The concept and position of NO fidelity has been removed and the position of sham treatment clarified.</p> <p>L168-176 (and Table 2)</p>
<ul style="list-style-type: none"> <li>Lack of consideration that a "minimal/low fidelity" (placement of arthroscopic camera and turn on fluid) placebo surgery control is not truly "low fidelity", as the introduction of saline lavage can remove inflammatory mediators, improve joint homeostasis, and improve the joint milieu.</li> </ul>	<p><b>R10:</b> Agree with reviewer... (to some extent). The capability to identify the theoretical "critical surgical element" of the surgery can indeed pose some difficulties in defining "fidelity" of the placebo intervention to the surgery (such as in the case given). However, that said, there is nearly always a more concrete theoretical basis and justification of the surgery than just "the introduction of saline lavage to remove inflammatory mediators to improve joint homeostasis, and improve the joint milieu". It is unlikely surgery would be sanctioned and performed with this as the primary purpose. A line has been added to account for this issue but we do not wish to confuse the new schema on fidelity.</p> <p>L177-179</p> <p><i>Added text:</i></p>

	<p><i>"It should be noted that this working framework is dependent on the theoretical premises of the operation and postulation of a "critical surgical element". This is not always possible, especially with surgeries that create effect by a multi-modal or dependent set of procedures."</i></p>
<ul style="list-style-type: none"> <li>Need more discussion of independent, experienced, world-renowned surgeon evaluation of the quality of the surgeries performed. If efficacy design in a homogenous sample, then that "can it work" mandates the best surgeons, similar to your use of "best non-operative care". An evaluation of surgical quality of all surgeries performed would validate the techniques used.</li> </ul>	<p><b>R11:</b> This is an interesting point and placebo control trials should not reflect a heavily pragmatic design. If information on mechanism is required (and mostly it is from these studies) then the surgery should have a definite minimum quality and be performed by experienced surgeons. We have stated this previously but have added a further line to clarify.</p> <p>L466-470</p> <p><i>The issue of quality control also arises for the surgical procedure. If information on mechanism is required (and it mostly is from these studies) then the surgery should have a definite minimum quality and be performed by experienced surgeons. The "can it work" question tends to trump the "does it work" question and this mandates the use of highly competent surgeons. Evaluation of surgical quality of all surgeries performed in such studies may be needed for validation.</i></p>
<ul style="list-style-type: none"> <li>No discussion of blinding index, in which patients may be able to determine their group allocation prior to study completion.</li> </ul>	<p>There are very mixed views in the literature on the appropriateness of using the blinding index. The CONSORT statement 2010 on the reporting of randomised controlled trials (<a href="http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Explanation%20and%20Elaboration%20Document-BMJ.pdf">http://www.consort-statement.org/Media/Default/Downloads/CONSORT%202010%20Explanation%20and%20Elaboration%20Document-BMJ.pdf</a>) also stresses the methodological difficulties with such testing of the "success" of the blinding and do not advocate that it be done. It notes "Because participants and healthcare providers will usually know whether the participant has experienced the primary outcome, this makes it difficult to determine if their responses reflect failure of blinding or accurate assumptions about the efficacy of the intervention. Given the uncertainty this type of information provides, we have removed advocating reporting this type of testing for blinding from the CONSORT 2010 Statement."</p> <p>Given this wider ongoing debate about the appropriateness (or not) of testing for blinding, we would prefer not to stray into the discussion of testing/not testing for blinding in this paper as it is not core to the primary focus.</p>
Line by line analysis:	

<ul style="list-style-type: none"> <li>• Abstract:</li> <li>• P2:</li> <li>• Well written, concise. Directly states the purpose of the submitted review.</li> </ul>	Thank you
<ul style="list-style-type: none"> <li>• Introduction and Background:</li> <li>• P2:</li> <li>• Briefly discusses reasons for impetus of the review. Well done.</li> </ul>	Thank you
<ul style="list-style-type: none"> <li>• What is a "placebo" in the context of surgical trials?</li> <li>• P4: for clarity for the reader, the penultimate and final paragraphs of this section contradict Table 2 - in the text, sham is "low fidelity". However, in Table 2, it is "no fidelity". Please resolve.</li> </ul>	<p>Thank you. Amended. See R9. We have virtually omitted the use of "sham" for clarity.</p> <p>L168-176</p>
<ul style="list-style-type: none"> <li>• When are placebo surgical controls acceptable?</li> <li>• P7:</li> <li>• Unsure why nomenclature of "best" nonoperative care, which is actually used twice in the same sentence), is used - the implication to surgery is ambiguous and misleading. If we are using adjectives to qualitatively subjectively describe treatments, then why don't you call it "best" operative care - there are good and bad surgeons, just as there are good and bad non-surgical physicians, physiotherapists, etc. Either remove "best"</li> </ul>	<p>Response as above. Addressed.</p> <p>L327-328</p>

<p>from this section (and all other sections similarly used), or add the same descriptor the surgery groups.</p>	
<ul style="list-style-type: none"> <li>• Trial conduct issues for placebo surgical trials</li> <li>• P9: would be helpful for the reader to discuss potential selection bias upon willingness to be possibly randomized to the placebo group, despite complete educated informed consent process. The innate thought that the patient may not receive any benefit, and could potentially have a complication (morbidity, mortality, adverse event), in most normal able-minded adults, for the potential benefit of society, precludes participation. Thus, those that do participate may be of different stage in mental wellness. It is very well known that psychiatric wellness is a critical perioperative issue, as individuals with mental health disorders do less well following most elective surgical interventions. Similarly, pain can have significant effects on mental wellness. Pain can</li> </ul>	<p><a href="#">Response as above. In R2.</a></p>



<p>influence trial participation decision making for patients. At a minimum, a demographic statistical comparison of the two (or more) groups (enrolled and randomized versus declined for standard care).</p>	
<ul style="list-style-type: none"> <li>• Similarly would be helpful to briefly discuss genetic analysis for propensity to respond to a placebo surgery (COMT, OPRM-1, CB1, CB2, TPH2, 5HTTLPR, among several other known biomarkers). Although randomization should mitigate the possible distribution of all placebo responders in one group and none in another group, it can still happen - and without measurement of these characteristics, the true placebo effect is unknown.</li> </ul>	<p><a href="#">Response as above for R1.</a></p>

<ul style="list-style-type: none"> <li>• Interpretation and translation into change of policy and practice</li> <li>• P10: last sentence of the page - "advice for patients" - please add further context - if there are only two study arms - one placebo surgery and one "real" surgery, without a natural history "no treatment" model, and the patient has already tried non-surgical care and is still significantly symptomatic, what do you do? How do you manage that clinical encounter? The patient doesn't care what you do in the operation, they just want to feel better. Thus, if a "real" or if a placebo surgery works, that's all they care about. How do you reconcile this issue?</li> </ul>	<p><b>R12:</b> This is a useful point but perhaps steps outside the remit of the work. We have added the following for completeness:</p> <p><i>Added Text: Advice for patients should include information about the likely benefits of both the definitive and alternative treatments. This paper has not addressed the [controversial] merits of offering placebo treatment (surgery) as a definitive intervention. Such an option is only possible if there are sufficient potential healthcare gains observed with placebo intervention.</i></p> <p>L521-522</p>
<ul style="list-style-type: none"> <li>• References:</li> <li>• Only 15/45 are within past five years.</li> </ul>	<p>We note this comment, but wished to include many of the seminal papers in the field, many of which were published more than five years ago.</p>
<p><b>REVIEWER #2:</b></p>	
<p>Beard and colleagues present a review on the use of placebo control in surgical trials. The manuscript is structured into the following sections: (i) introduction; (ii) definition of placebo in this context; (iii) acceptability of placebo; (iv) risk; (v) trial conduct issues; and (vi) interpretation. The main message is that placebo-controlled trials on surgical</p>	<p>Many thanks for a set of well thought out suggestions and comments.</p>

interventions may be justifiable in some situations and that the degree of fidelity to the investigational surgery is an important consideration. A checklist is included to help with design of such trials.	
The topic is of interest and the issues addressed are ethically complex and not easy to resolve. The paper is generally well written. I have the following comments:	
<p>1. The issue of equipoise is arguably central to the consideration of whether or not a placebo control is justifiable. In this context, brief discussion about the complexity of establishing equipoise would be germane to the discussion. The paper of Miller et al. provides extensive discussion on the problem of agreement in relation to what constitutes equipoise (Miller FG, Joffe S. Equipoise and the dilemma of randomized clinical trials. N Engl J Med 2011;364(5):476-80).</p>	<p><b>R13:</b>  We agree that equipoise is one of the key issues in the ethics of placebo RCTs in surgery. We now emphasize this point: Added text: <i>"Ethical standards suggest, however, that exposing research participants to such risks is allowed provided equipoise exists among the study arms, study harms have been minimised and are acceptable to the participant."</i> Miller and Joffe (2011) take the view that equipoise would not permit placebo RCTs when a surgical procedure is in common use. Hey et al. (2016) argue that this misconstrues equipoise, because the relevant uncertainty is the state of evidence, not opinion or practice. We have added this important clarification, saying that <i>"Disagreement or uncertainty should be understood in terms of the state of evidence rather than unsubstantiated opinion."</i> And with regard to examples such as vertebroplasty, <i>"Although the surgical procedure is commonly used, equipoise exists because of the lack of supporting evidence."</i></p> <p>L180-L258</p>
<p>2. The central ethical issue to be considered from a patient perspective relates to the degree of risk that the patient is exposed to. In contrast to placebo-controlled medicines trials (where the main risk is that the patient does not receive the active treatment and no or minimal risks are expected from the placebo tablet per se),</p>	<p><b>R14</b>  We agree with the reviewer that the assessment of scientific value is key to the ethical analysis and have added a description of a systematic approach to the assessment of value and validity by Binik and Hey (2019). We now say: Added text: <i>"Research ethics committees commonly struggle with the assessment of scientific value, and use of the "value-validity framework" is recommended. The assessment of scientific value requires that (1) the research question is clinically important, (2) the hypothesis is justified by the current state of evidence, and (3) the study is well situated in a research portfolio."</i></p> <p>L224-227</p>

<p>the patient is exposed to a definable and foreseeable degree of risk due to the "sham" procedure, without any prospect of benefit for the individual. In this respect, only the greater societal value can compensate for the risk assumed at an individual patient level. This issue requires more attention and is a critical element of informed consent. For example, more detailed discussion of mechanisms to evaluate the "social value of the study" should be provided.</p>	
<p>3. By considering patients' preference in the study design, it may be possible preferentially to enrol patients who are actively demanding a surgical therapy. This issue might be explored and discussed.</p>	<p><b>R15:</b> A reasonable point. This pre-existing bias might exist. Such a feature would not be present when there is a non-surgical or no treatment comparison required. Again with limited space we have not included substantial changes at this time (but modified the wording). If the Editor wishes this to be addressed in more detail we can include but such discussion may be substantial.</p> <p>L425-429</p>
<p>4. Against the background of the complex ethical issues at hand, in these types of trials, it is particularly important that the clinical trial has the greatest possible chance to answer the primary research question in a robust manner (high internal validity) with high generalizability for the relevant clinical community (high external validity). This should be emphasized in the discussion.</p>	<p><b>R16:</b> Agree. We believed we had addressed this but there was room for amplification. We have added to the key message.</p> <p>Added Text:</p> <p><i>Against a complex set of ethical issues, it is particularly important that these trials have the greatest possible chance to answer the primary research question in a robust manner (high internal validity) with high generalizability for the relevant clinical community (high external validity)</i></p> <p>L528-531</p>
<p>5. In assessing the ethics of sham-controlled RCTs, institutional review</p>	<p><b>R17</b></p> <p>We thank the reviewer for this point. We are unaware of any guidance and would welcome specific suggestions. We believe</p>

<p>boards are faced with the challenge of weighing the foreseeable and preventable harm of a placebo procedure against the risk of mistakenly believing an invasive procedure or implant to be useful when it is actually not. Are there any specific guidelines for institutional review boards dealing with this issue? Perhaps detail could be included if available.</p>	<p>that the possibility of therapeutic misconception is best addressed through evidence-based changes to the informed consent process that have been shown to improve research participant comprehension. First, placebos must be clearly identified as lacking evidence -based prospect of direct benefit and language that may unwittingly mislead participants must be avoided. Second, consent forms should be simplified and adequate time for one-on-one discussion provided. Third, research participant comprehension should be judged as appropriate. We have now added language emphasizing that [added text]</p> <p>Added text:  <i>As placebo surgical trials provide a potentially nontherapeutic intervention additional protections may be indicated. It is important to ensure adequate patient comprehension of the likely (lack of) benefit from placebo allocation to reduce therapeutic misconception.</i></p> <p>L241-244</p>
<p>6. The authors suggest that the placebo effect can be mediated by conditioning and response expectancy. A third factor, experience of the health care interaction itself, has also been identified as contributing to placebo effect and might be mentioned (Jubb J, Bensing JM. The sweetest pill to swallow: how patient neurobiology can be harnessed to maximise placebo effects. <i>Neurosci Biobehav Rev</i> 2013;37(10 Pt 2):2709-20; and Di Blasi Z, Harkness E, Ernst E, Georgiou A, Kleijnen J. Influence of context effects on health outcomes: a systematic review. <i>Lancet</i> 2001;357(9258):757-62).</p>	<p>An initial draft (and the accompanying NIHR report) contained greater neurobiology and more detailed descriptions of conditioning. However, once again in view of word limit and reference limit it was decided this might not be seminal to guidance for researchers setting up, conducting and reviewing placebo trials in surgery (one of the main purposes of this paper). We have omitted in this particular work but will include more in the NIHR MRC report.</p>
<p>7. The authors may wish to include mention of the Hawthorne effect in</p>	<p>Response as above (to point raised by referee 1 about Hawthorne) – R8.</p>

<p>relation to its potential to impact on outcomes in both investigational and treatment arms (Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ 2015;351:h4672).</p>	
<p>8. It might be illuminating to mention and discuss the ORBITA trial (Al-Lamee et al., Lancet 2017) in the paragraph relating to identification and mitigation of risk. This trial has many similarities with a placebo-controlled trial of surgical interventions, and might be a useful reference for the reader with a surgical background. Although the primary results of that trial have received widespread attention from many stakeholders involved in that field (in line with the issues mentioned in the section on interpretation and translation on page 10), analysis of serious adverse events, shows that these were considerably higher in the placebo or sham-controlled arm (8 events vs. 0 events, see data in supplementary material of that trial).</p>	<p><b>R18</b> Sensible addition for balance. Now included. [Added text]</p> <p><i>This issue is highlighted by trials such as the ORBITA study in interventional cardiology. The placebo group were in this case found to have a greater number of adverse events than the normal treatment leading to difficulties and contention in interpretation.</i></p> <p>L364-367</p>
<p>9. It would be useful to include a text box indicating the methods that were used in searching the literature for the present manuscript.</p>	<p><b>R19:</b> Completed and added.</p> <p>The methods used to search the literature are reported fully in paper reporting the systematic review update, which is currently accepted with minor revisions by the Journal of Clinical Epidemiology. We include a summary of these methods in the attached text box with reference to the full paper. It is expected the paper will be accepted fully by the end of November 2019</p>

	L262
10. Assessment of the success of blinding is essential in trials with placebo control. This issue should be mentioned and relevant citation included.	Response as above (re measuring blinding via blinding index raised by reviewer 1).
11. Additional detail should be provided for the reviewer on the systematic review that was conducted. It is not helpful to refer the reader to a paper that is in preparation. In my opinion, at least an appendix table listing the included studies and their characteristics should be provided as supplementary material to the present paper.	<p>R20: This has been provided.</p> <p>As above, we have now had the paper reporting the systematic review in full accepted with minor revisions by the Journal of Clinical Epidemiology. It is expected that the paper will be accepted fully by the end of November 2019. We now include an appendix table listing included studies and their characteristics, with reference to the full paper.</p> <p>L263</p>
REVIEWER #3	
Name: Teppo Järvinen	
Position: Professor of Orthopedics and Traumatology	
<p>Comments for the Authors</p> <p>Thank you very much for asking me to review this interesting paper entitled: "Considerations and Methods for Placebo Controls in Surgical Trials: State of the Art Review and ASPIRE Guidance".</p> <p>The objective of the paper - to provide a summary of current knowledge on placebo controls in surgical trials - is a very interesting one and of utmost importance/interest to the entire surgical discipline at large. Of all surgical disciplines, orthopaedics is probably the one that has been most affected by the increased popularity of this</p>	<p>Many thanks for your detailed and highly considered comments. It is clear a considerable amount of time has been spent on this review (actually by all reviewers) and the expertise in this area is very evident.</p>

<p>trial design. A seminal paper published in 2002 (Moseley, O'Malley et al. 2002), assessing the efficacy of arthroscopic debridement for knee pain in osteoarthritic patients, pushed the entire field of orthopedics into turmoil: Using a placebo-surgery controlled design, the authors provided unprecedentedly robust evidence that questioned the viability of this enormously common orthopedic surgery. This brought along a realization that not all of our clinical practices - although being intuitively highly rationale - stand the scrutiny of robust scientific testing. The trial and its findings also prompted a major revolution in the way we now test our practices, as a considerable number of our popular procedures only have low quality (high risk of bias) evidence - at best - to support the practice.</p> <p>Undoubtedly, the group gathered for the task of developing the guidance possesses the experience and knowledge to provide a premier scientific contribution on the topic.</p> <p>I have now spent quite a considerable amount of time to thoroughly review the paper. Below please find my comments.</p>	
MAJOR COMMENTS	
<p>Having been involved in the design and execution of three placebo-surgery controlled trials, my major intellectual challenge has always been - and after reading this paper, still remains - the question as to what is the primary purpose of these placebo-surgery</p>	<p><b>R21:</b> This is an insightful point, has been the point of much discussion and many of the group do have some sympathy.</p> <p>First, it is felt we are in agreement about the purpose being the evaluation of surgery (taking account of the placebo effect). There is no attempt to include the evaluation of the effect of placebo (hence the reduced neurobiology aspect). This has been further emphasised in the draft.</p>



<p>controlled trials? The authors start their paper (1st sentence of the abstract) by saying "... assessing the efficacy of surgical interventions". My take on the question is exactly the same: Placebo-surgical trials should be restricted for this purpose, only. However, when reading through the paper, I can't help to think that the authors seem to be suggesting that these trials can (should) also be used to study the potential "placebo effect" of surgery - an assertion that stems from their desire to include a "no treatment" group. Such desire is obviously both highly scientifically ambitious and intuitively rationale, but in my opinion, has two fundamental flaws that... have convinced me to abandon the idea. Namely:</p>	<p>In regard to 2 or 3 group designs, and inclusion of a no treatment group – we have already included a section on this (<i>Should a placebo-surgical trial have a no intervention arm</i>) but the points raised may require some minor adjustment (which have been completed).</p> <p>The main issue here is whether demonstration (using a 2 arm study – placebo v normal surgery) that the mechanism by which the surgery was thought to provide effect is proven wrong, and that this evidence is then sufficient to make inferences about lack of benefit for surgery overall. There is a difference of opinion here (particularly by surgeons) and some feel that the benefit of surgery should be evaluated outside the known mechanism (i.e. a “black box” effect approach can sometimes be acceptable).</p> <p>For example in a 3 arm placebo control trial, (which includes a no treatment arm), the comparison (and lack of effect) between any kind of surgery (placebo or normal) is often more informative than the comparison between the two surgeries.</p> <p>A comment in response from one of our co-authors is helpful.</p> <p><i>“I do sympathise to some extent with this reasoning, as I voiced during the Oxford meeting.</i></p> <p><i>In addition, these trials usually have to be done with ‘academic’ funding support and within ‘academic’ resources. There’s a considerable difference in resources and time needed between a 2-armed trial and a 3- or 4-armed trial. The latter may be ‘scientifically’ superior, but are they always needed?</i></p> <p><i>Perhaps a few words could be added on when 3- or 4-armed trials are really needed?”.</i></p> <p>In view of the contention and this sensible course, a few lines have been added.</p> <p>L323-355</p>
<p>1) Can we realistically assume to be able to carry out a placebo-surgical trial with a "no treatment group" and expect the findings of this particular group to be robust enough to truly quantify the placebo effect (and thus, justify its inclusion in the design), given that patients randomized to this group should be as symptomatic as those</p>	<p>This point is well made but examples have shown that patients are willing to be randomised to a 3 group trial – CSAW, KORAL ... probably others.</p> <p>Re KORAL – no issues were raised by patients about the no treatment group (it was called “non-operative management with specialist re-assessment”) – they were happy to be potentially randomised to that (that they would get specialist re-assessment anyway)</p>

<p>randomized to placebo surgery or the index surgery? In the end, as a surgeon, I have been trained to consider surgery the last resort after all other (nonoperative) means have failed. Under such circumstances, I find it hard to believe that highly symptomatic patients would be willing to sit back and wait for a period long enough to first be able to arrange and carry out the surgeries in the other groups and then also have a sufficiently long period of time for follow-up to obtain full recovery after surgery (which is the absolute necessity for robust inferences). Unless these premises are met, the inclusion of a "no treatment group" threatens to compromise the validity of the findings of the entire trial.</p>	<p>We believe the CSAW is an example where, while there were challenges associated with conduct and interpretation of the no treatment arm, its inclusion added value to the study overall and of the wider interpretation. The value of such an arm would likely be context specific and to an extent only assessable after the study has been completed. We have said this in the text but amplified.</p> <p>See <b>R21</b> above and in text.</p>
<p>Also, there is another, equally troubling issue regarding the "no treatment group", that is blinding (lack of it). Both the patients and the researchers may have different and even disproportionate expectations of benefit with regards to the different study treatments. In fact, it has even been speculated that when patients are told at entry about the possibility of surgical treatment but then allocated to non-operative or even "no treatment", so called 'failed opportunity' may make patients with residual symptoms less satisfied with their care and subsequently drive them to seek surgery (Dowrick &amp; Bhandari JBJS-Am 2012).</p>	<p><b>R22:</b> This point, also dealing with the two arm or three arm issue is also valid. A sentence on resentful demoralisation has been added.</p> <p>However, that said the “no treatment” arm has multiple purposes. We have added text as noted above which highlights other effects which a no treatment group will also undergo which may result in an observed change in outcome (such as the Hawthorne effect and regression to the mean).</p> <p>L350-351</p>
<p>Finally, I find it quite irrational that we first claim that the use of a placebo surgery comparator (vs. any other design) is</p>	<p>As above and see response below R23:</p>

<p>mandatory in order to adequately mask the patients, caregivers, outcome assessors, etc., and then we will immediately abandon this principle in asserting that lack of blinding does not compromise the validity of the comparisons between "no treatment" vs. other groups? To me, this is a circular argument, and as such, an intellectual fallacy but perhaps the authors are able to explain why my assertion is not valid. At least this part of the paper needs better justification.</p>	
<p>To showcase the above noted concerns, please allow me to use the only (?) trial that has set out to assess/quantify the surgical placebo as an example (the CSAW trial addressing the efficacy of subacromial decompression surgery, ref. #24 in the original submission) In this study, the investigators randomised 313 patients to three treatment groups: 106 to decompression surgery, 103 to arthroscopy only, and 104 to no treatment. Perhaps due to the imminent risk of high incidence of crossover from the "no treatment" group, the investigators chose 6 months as their primary outcome assessment timepoint. Due to this methodological choice, 24 [23%], 43 [42%], and 12 [12%] of the decompression, arthroscopy only, and no treatment groups, respectively, did not receive their assigned treatment by 6 months (at the primary outcome assessment timepoint!). And further, &gt;10% of those initially allocated to "no treatment" ended up having surgery by the 6-mo follow-up. As showcased by this study, many - if not all -</p>	<p><b>R23:</b> Crossover was indeed a negative issue with CSAW but this was considered against the merits of having the no treatment arm. Some of the authors (of this work) would indeed like to indulge in further detailed discussion of this particular trial (positive and negative) but other reviewers have suggested more balance in terms of speciality and study is required. We have aligned with the latter.</p> <p>However, we have added a sentence to address the main excellent point raised.</p> <p>L352-355</p>

<p>of the concerns expressed above materialised. As laudable as the effort by the CSAW investigators was from a scientific perspective, one needs to critically assess the true implications of the findings. Perhaps this paper provides a perfect venue for such thorough elaboration.</p>	
<p>2) Is it (ethically) justified to use placebo-surgery when there is already evidence to suggest that the index surgical procedure is no better than the best nonoperative treatment? Or do we require that surgery has "proven" superiority, but the evidence is questionable due to high risk of bias (low quality)? When looking back, quite a high percentage of previous placebo-surgery controlled trials (at least in orthopaedics) have been carried out under the circumstances that we have already had evidence to suggest that the studied surgical procedure is no better than the (best available) nonoperative treatment. Or at least the clinical meaningfulness of the alleged superiority/benefit is highly debatable. Should we still consider placebo-surgery design justified under such circumstances? One argument in favour of still being proceeding to carry out a placebo-surgery controlled trial is that surgery vs. nonoperative treatment trials are inherently of "low quality / high risk of bias" (although the bias, if surgical placebo effect does exist, should also skew the data in favour of surgery). Another similar argument would be that more robust evidence is required as the clinical practice still continues "unabated"</p>	<p>A complex philosophical point - which probably cannot be done justice with the available word count.</p> <p>In response to the reviewer; the main issue here is that many surgical procedures in general have been adopted and become common without adequate evaluation. Note we are trying hard to address this, particularly with new interventions coming on stream i.e. robotic surgery, AI. but still lag behind. The "power" of surgery (and ironically this is closely linked to its strong placebo effect) make any withdrawal of treatment difficult without evidence from influential and robust studies (such as FIMPACT and CSAW).</p> <p>If there is high quality evidence that surgical treatment is no better than non-operative treatment then absolutely no placebo trial is required.</p> <p>These issues are important and fascinating but maybe more political and outside the science reported here.</p> <p>We would respectfully request the editor to make a decision whether this particular area should be expanded. We are happy to do so but have already extended word count addressing many of these interesting points.</p>

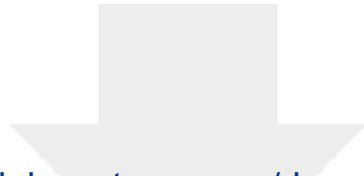
despite the evidence questioning the particular practice.	
<p>This brings me to my only other comment regarding the manuscript: The authors note "a long lag between evidence becoming available to a significant change in practice" on page 10, in the paragraph beginning "Experience with...". However, their knee arthroscopy example might not be completely accurate, as we have witnessed quite a dramatic de-implementation of knee arthroscopy (in a range of 50-70% from the highest volumes) in many countries, such as Finland, Sweden, Norway, Denmark, the Netherlands, and even the US. Strictly speaking, the trial by Moseley et al. (NEJM 2002) showed arthroscopic debridement futile in patients with advanced OA - most patients undergoing knee arthroscopy are treated with arthroscopic partial meniscectomy (APM, a completely different procedure) and have early knee OA. Therefore, a clear medical reversal may not have been required until the publication of a series of other trials proving APM futile, which took place between 2011-2017.</p>	<p><b>R24:</b> We agree the evidence for implementation (with hard data) is not strong. However, it has taken some time for arthroscopy for OA to become considered inappropriate. The real point being made is that there is often resistance to uptake of the new evidence. We have softened the language.</p> <p>L497</p>

<p>4) Ethics: Page 3, second para.: "Some information on the ethical implications of surgical placebo trials is available 7- 12." I respectfully feel compelled to state that this sentence undermines the prior ethical analyses on the use of placebo-surgery, which - at least to me - are quite exhaustive and quite thoroughly address many of the ethical dilemmas related to the use of the design. I have particularly found the work by Franklin Miller useful, so perhaps in addition to ref. #11, the authors should consider adding this reference (Miller FG. Sham surgery: an ethical analysis. Sci Eng Ethics 2004;10:157-66) as according to my understanding, this is the very first paper that outlines the "6 key ethical question" procedure/protocol that should be carried out to ensure that the (placebo-surgery controlled) trial designed is ethically sound. In essence, I think it would only be fair to give credit to those that have truly pioneered the field. And perhaps even consider adding this set of key ethical question in the paper (re: Page 5, "a two-step ethical analysis") and figure 1?</p>	<p><b>See R13 and R14:</b> Absolutely not our intention to exclude previous relevant work – indeed the work of Miller was very influential in our discussions. The ethics group have addressed this above is response to other reviewers.</p> <p>We thank the reviewer for drawing our attention to this omission. We have added reference to this important article. Miller’s work, including the six key ethical questions, informed our discussions, and we do cover the issues addressed by his questions. We diverge from Miller’s project in two ways. First, we believe equipoise is central to the question of the ethical permissibility of placebo trials in surgery and argue that it permits important RCTs to proceed (Savulescu et al. 2016; Hey et al. 2016). Second, following on early work in the field (Weijer, 2002), we view the surgical placebo as a complex procedure, and this idea is foundational to our novel ethical analysis.</p>
MINOR COMMENTS	
<p>1) Page 3, bottom of the page: "Any imbalance in the tone and quantity of information given about the benefits of the index procedure compared to that given for the placebo control can be stark and can influence outcome 19." I am inclined to think that any imbalance in the way/tone/whatsoever given between any two treatment</p>	<p>Thank you for highlighting. Probably yes, retain this piece. There have been historical examples where the consent or Patient Information Sheet may not be optimal and unbalanced. We want to emphasise this point for those starting out in placebo surgical trials.</p>

<p>groups can influence the outcome of any trial. Isn't this why patients should be explicitly informed about all the treatments, their anticipatable benefits and harms, etc.? Is this sentence truly needed?</p>	
<p>2) Page 4, 1st sentence after the title "WHEN ARE...": "Surgical placebos may be most appropriate where the benefits of surgery are not life-saving,..." I have a difficult time understanding this sentence, as it - in my opinion - implies that the surgical procedure "excluded" are those proven to be life-saving...? Perhaps this should be rephrased to state, e.g., "Surgical placebos may be most appropriate where there is poor evidence on the efficacy of the procedure and a justified concern that the results of an open trial would be associated with high risk of bias.</p>	<p><b>R25:</b> Excellent suggestion. Rephrased.</p> <p><a href="#">L181-184</a></p>
<p>3) Page 7, 2nd para.: "For interventions which may have a significant placebo effect a guideline producer would like to see robust studies which explore that effect (such as a three arm study comparing active intervention, placebo, and usual care - discussed below)." Frankly, I don't understand the rationale behind this comment. Why would a guideline producer want/need exploration of a possible placebo effect, as long as there is robust evidence to show that the index surgery is clinically meaningfully superior to both placebo and best nonoperative care. See also MAJOR COMMENTS.</p>	<p><b>R26.</b> Agree: We have rewritten the paragraph (and have provided associated references) to more clearly indicate why guideline producers, such as the UK National Institute of Health and Clinical Excellence, specify why they wish to see the exploration of the placebo effect. The re-written text is as follows ...[changed text]</p> <p>“Often guideline producers want to understand how a health gain is generated, and often feel uneasy when a gain is mainly generated through a non-specific placebo mechanism rather than the anticipated anatomical, physiological and psychological processes that the intervention’s logic model may suggest. This is particularly important where a placebo effect may only exist because of a trial [Ernst]. For interventions which may have a significant placebo effect a guideline producer would like to see robust studies which explore that effect (such as a three arm study comparing active intervention, placebo, and usual care – discussed below). This enables them to explore any placebo effect which may inform the guidelines produced, will help inform a payer's decision whether to reimburse a treatment, and suggest</p>

	<p>further research to explore or modify the intervention [NICE, Cochrane].”</p> <p>L317-321</p>
<p>4) Page 7, next section entitled: "Should a placebo-surgical trial have a no intervention arm?" See my previous question and MAJOR COMMENTS.</p> <p>Also, "A no intervention arm has the advantage of measuring the natural history of the condition without any treatment." Unfortunately, I beg to differ. As noted above, this group (comparison to surgically treated groups) is compromised by a myriad of potential biases.</p>	<p>Response as per above on no treatment (R21).</p>
<p>5) Page 7-8, re: risks: Perhaps the authors should also consider adding a brief notion that unless a sufficiently robust trial is carried out and the surgery continues unabated, all patients are subjected to all risks related to the procedure. In this situation, the more risky the procedure, the more urgent the need for a sufficiently robust (placebo-surgical) trial.</p>	<p>R27: Another useful addition. Now included.</p> <p>L395-397</p>



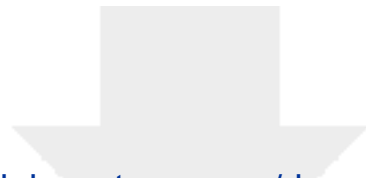


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